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CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE

BONE, REPRODUCTIVE AND UROLOGIC DRUG

ADVISORY COMMITTEE (BRUDAC)

AND THE DRUG SAFETY AND RISK MANAGEMENT

ADVISORY COMMITTEE (DSaRM)

Thursday, June 4, 2015

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Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

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P R O C E E D I N G S

(7:30 a.m.)

Call to Order

Introduction of Committee

DR. LEWIS: Good morning. I'd like to ask everyone to take their seats so that we can get started. We have a very full agenda.

Welcome to the Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. My name is Vivian Lewis, and I'm the acting chair of the Bone, Reproductive and Urologic Drugs Advisory Committee.

I'd like to remind everyone first to please silence their cellphones, smartphones, and any other devices if you haven't already done so. I'd also like to identify the FDA's press contact, Andrea Fischer. Andrea, could you please, yes, wave over there.

We'd like to ask everyone to introduce themselves. I'm going to start with the FDA staff members please.

DR. BEITZ: Good morning. My name is Julie Beitz. I'm the director of the Office of Drug Evaluation III in CDER FDA.

DR. JOFFE: Hylton Joffe, director of the Division of Bone, Reproductive and Urologic Products at FDA.

DR. NGUYEN: Good morning. I'm Christine Nguyen. I'm the safety deputy director in the Division of Bone, Reproductive and Urologic Products, FDA.

DR. CHANG: Good morning. Christina Chang, clinical team leader in the division.

DR. EASLEY: Good morning. I'm Olivia Easley. I'm the medical reviewer for safety for this application in the Division of Bone, Reproductive and Urologic Products.

DR. SEWELL: Good morning. I'm Catherine Sewell. I'm the medical reviewer for efficacy in the Division of Bone, Reproductive and Urologic Products.

DR. LEE: Hi. I'm LaiMing Lee, clinical pharmacology reviewer from the Division of Clinical

Pharmacology III, Office of Clinical Pharmacology.

DR. MANZO: Good morning. I'm Claudia Manzo. I'm the acting director of the Office of Medication Error Prevention and Risk Management, FDA.

DR. LEHRFELD: Good morning. Kim Lehrfeld. I'm a team leader in the Division of Risk Management within the Office of Surveillance Epidemiology here at the FDA.

DR. LINCOFF: Good morning. I'm Michael Lincoff. I'm a cardiologist at the Cleveland Clinic and on loan from Chronic Renal Drugs, where I'm the chair.

DR. BESCO: Good morning. My name is Kelly Besco. I'm a medications safety officer for the OhioHealth Healthcare System in Columbus, Ohio.

DR. GERHARD: Good morning. Tobias Gerhard, pharmacoepidemiologist from Rutgers University.

DR. PERRONE: Good morning. I'm Jeanmarie Perrone. I'm an emergency physician and medical toxicologist from the University of Pennsylvania.

MS. SHAW PHILLIPS: Good morning. Marjorie Shaw Phillips, Georgia Regents Medical Center and the University of Georgia, College of Pharmacy.

DR. STURMER: Good morning. Til Sturmer, pharmacoepidemiologist, University of North Carolina Chapel Hill.

DR. WHITAKER: Good morning. I'm Amy Whitaker. I'm a gynecologist at the University of Chicago.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm with the Division of Advisory Committee and Consultants Management.

DR. CURTIS: Good morning. I'm Kate Curtis. I'm a health scientist in the Division of Reproductive Health at the Centers for Disease Control and Prevention in Atlanta.

MS. ARONSON: Good morning. I'm Diane Aronson. I'm the patient representative.

DR. ALEXANDER: Caleb Alexander, Center for Drug Safety and Effectiveness at Johns Hopkins.

DR. BAGIELLA: Emilia Bagiella. Good morning. I am a biostatistician from the

Icahn School of Medicine at Mount Sinai in New York.

MS. BELL-PERKINS: Good morning. Elizabeth Bell-Perkins here as acting consumer rep.

DR. ORZA: Good morning. I'm Michele Orza with the Patient-Centered Outcomes Research Institute, and I'm an acting consumer representative today.

DR. GUESS: Good morning. I'm Marsha Guess. I'm a urogynecologist at Yale School of Medicine at New Haven, Connecticut.

DR. HANNO: Good morning. I'm Phil Hanno, urologist at the University of Pennsylvania.

DR. HEIMAN: Good morning. Julia Heiman, Indiana University and Kinsey Institute.

DR. BRANDON: Good morning. Marianne Brandon. I'm a clinical psychologist and sex therapist in private practice.

DR. JOHNSON-AGBAKWU: Good morning. My name is Crista Johnson-Agbakwu. I'm an obstetrician gynecologist, University of Arizona College of Medicine Phoenix.

DR. LEGGIO: Good morning. I'm Lorenzo Leggio. I'm a physician and a clinic investigator at the NIH Intramural Research Program.

DR. WEINFURT: Good morning. I'm Kevin Weinfurt, a psychologist at the Duke Clinical Research Institute.

DR. GELLAD: Good morning. Walid Gellad. I'm an internist at the University of Pittsburg.

DR. FLYNN: Good morning. Kathryn Flynn. I'm a health services researcher. I'm at the Medical College of Wisconsin.

DR. SILBERGLEIT: Robert Silbergleit. I'm an emergency physician and a clinical trialist at the University of Michigan.

DR. GORDON: Keith Gordon. I'm with Merck. I'm the industry representative.

DR. LEWIS: Thank you, all, and welcome. I'd now like to ask Dr. Bhatt to please read the Conflict of Interest Statement.

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration

is convening today's joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to

special government employees and regular federal employees who have potential financial conflicts when it's determined that the agency's need for a particular individual service outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, the members and temporary voting members of these committees have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C., Section 208, their employers.

Their interests may include investments, consulting expert witness testimony, contracts, grant, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of new drug application 22526 flibanserin 100 milligram tablets, submitted by Sprout Pharmaceuticals Incorporated, proposed for the treatment of hypoactive sexual disorder, HSDD, in

premenopausal women. This is a particular matters meeting during which specific matters related to Sprout's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Keith Gordon is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Gordon's role at this meeting is to represent industry in general and not any particular company. Dr. Gordon is employed by Merck & Company.

We would like to remind members and temporary voting members that if the discussions

involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusions will be noted for the record.

FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. LEWIS: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We do look forward to a productive meeting.

In the spirit of the Federal Advisory

Committee Act and the government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place only in the open forum meeting.

We're aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of the meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the topic during breaks or lunch. Thank you.

I'd now like to turn it over to Dr. Joffe to make some introductory remarks.

FDA Opening Remarks

DR. JOFFE: Good morning, everybody. What I'd like to do over these next 15 minutes is provide an overview of the objectives of today's meeting; provide some background and regulatory history;, introduce the efficacy and safety issues that you'll be hearing about later over the course of the day; summarize today's schedule; and give a preview of the discussion and voting questions so

that the committee members can start framing the issues as they hear the presentations and discussion.

I'd then like to summarize the current landscape of medications approved for treating sexual dysfunction in the United States, and then I'll offer some concluding remarks.

So today's objectives are to obtain independent expert advice from a multidisciplinary advisory committee on whether the benefits of flibanserin outweigh its risks. We also wish to obtain input from stakeholders such as patients and patient safety advocates.

Flibanserin is a 5-hydroxytryptamine type 1A receptor agonist and a type 2A receptor antagonist. It's a new molecular entity. It's not approved in any country. The applicant is proposing treatment for hypoactive sexual desire disorder or HSDD. They're seeking approval only in premenopausal women.

HSDD is characterized by absent or deficient sexual fantasies and desire for sexual activity

that causes marked distress or interpersonal difficulty and is not better accounted for by other conditions or medications.

The applicant is proposing 100-milligram tablet, which will be taken daily at bedtime. After exposure, the half-life is about 12 hours, and maximal concentrations occur about 45 minutes after the pill is taken.

There are no approved treatments for HSDD, so this is an unmet medical need because FDA believes there are patients who could benefit from a safe and effective treatment.

Regulatory history. This is the third review cycle for this application and the second advisory committee meeting. The first advisory committee meeting was held in 2010. Ten of the 11 committee members at that time voted that there was insufficient evidence of efficacy.

At the time, there were 2 phase 3 trials, and the trials showed an effect on a secondary endpoint that measured desire using the FSFI instrument or the Female Sexual Function Index

instrument. But both trials failed on their co-primary endpoint that assessed desire daily with an electronic diary.

There was unanimous vote at that time against approval citing this insufficient evidence of efficacy given the loss on the co-primary endpoint and also safety concerns including somnolence, drug interactions, and an interaction with alcohol.

After the advisory committee meeting, FDA issued a complete response letter, which is a letter that explains why FDA could not approve the application in its current form. Some, but not all, of FDA's concerns are shown on this slide.

There was lack of substantial evidence of efficacy for reasons I explained previously. The letter also noted overly restrictive entry criteria into the phase 3 trials, raising questions about generalizability of the findings to the intended population. There was also a further need to evaluate interactions with some CYP3A4 inhibitors and inducers. The letter also requested a

dedicated interaction study with alcohol.

FDA also recommended a new phase 3 trial that used less restrictive entry criteria, and said that if the applicant chose to use an instrument for desire for the co-primary endpoint that differed from what was used in the prior two trials, the daily desire with an electronic diary, that this new instrument should have acceptable content validity and measurement properties.

After this first review, the applicant, Boehringer Ingelheim, sold the application to Sprout Pharmaceuticals, which is the current application holder. Sprout resubmitted the application and responded to the first cycle deficiencies, and the resubmission included a new phase 3 trial that used FSFI as the co-primary endpoint for assessing desire.

After a careful review, FDA determined that the application was still not approvable, and some, but not all, of FDA's comments in that letter are shown on this slide. FDA noted a numerically small treatment effect that did not clearly outweigh the

risks. There were some residual concerns with content validity with the FSFI instrument.

There were cases of hypotension and syncope in some subjects who were also using alcohol, and there were cases of syncope and hypotension in some subjects who were also using moderate or strong CYP3A4 inhibitors.

The letter also noted events of central nervous system depression such as somnolence or sedation, some that were temporarily associated with accidental injury.

So the second complete response letter requested some additional studies including a driving study to assess whether the effects on the central nervous system persisted to the following day given the long half-life of the drug. We also asked for additional clinical pharmacology studies to better characterize the metabolism of flibanserin, and you'll hear why we requested that in later presentations.

The letter also stated that after the applicant has addressed or responded to these

deficiencies, that an advisory committee meeting would be warranted to discuss whether the benefits outweigh the risks.

The applicant, after receiving our letter, appealed the decision to Dr. Jenkins, our director in FDA's Office of New Drugs. Sprout stated that FDA had erred in its assessment and requested the application be approved without additional studies.

Dr. Jenkins denied the appeal, stating that FDA's assessment was sound and did not deviate from precedent. But Dr. Jenkins recommended that the applicant address the complete response letter concerns and that that would help to better inform benefit/risk, and he also fully agreed with taking the application to advisory committee.

Efficacy and safety. This slide summarizes, at a high level, the key efficacy findings. You'll be hearing more about this over the course of the day. For satisfying sexual events from a baseline of about 2 or 3 episodes per month in the pivotal trials, women had an improvement with flibanserin of about 0.5 to 1 additional episode per month

compared to placebo.

For desire assessed with the FSFI instrument, there was a baseline of about 1.8 to 1.9, and the woman had a mean improvement of about 0.3 to 0.4 compared to placebo, and that's on a scale of 1.2 to 6.

For distress, the baseline was 3.2 to 3.4, and flibanserin resulted in a mean improvement of 0.3 to 0.4 over placebo, and this is on a scale of zero to 4. It is notable that there's a sizeable placebo effect in the phase 3 trials.

All these treatments are statistically significant, and FDA is seeking input as to whether these observed treatment effects outweigh the risks.

You'll be hearing about safety in detail later on. Here, I want to mention the major safety concerns of hypotension and syncope, central nervous system depression, and accidental injury. Hypotension, syncope, and central nervous system depression all occur with flibanserin alone. They're also exacerbated when flibanserin is taken

with alcohol, and they're also exacerbated by moderate or strong CYP3A4 inhibitors.

To ensure we have sufficient expertise, we've assembled an advisory committee that's joint with the Drug Safety and Risk Management Committee. As you've heard, we've supplemented it with additional expertise. Some members also have expertise in sexual medicine, patient-reported outcome assessments, alcohol use, cardiology, emergency medicine, pharmacoepidemiology, and internal medicine.

When I finish, the applicant will present for about an hour and 10 minutes. There will then be an opportunity for the panel to ask clarifying questions to the applicant for about 30 minutes. After a short break, FDA will have its presentation with opportunity after that for clarifying questions from the panel to the FDA.

We'll then have lunch, and then we have our open public hearing, which is almost always one hour in duration. For today, we've extended the open public hearing to an hour and 45 minutes to

accommodate the overwhelming interest in folks who wanted to sign up to speak. After that, there will be one more round of clarifying questions, and then about three hours of committee discussion and voting.

So here are the discussion and voting questions. The first discussion question asks the committee to comment on the clinical significance of the observed placebo-corrected treatment effects of flibanserin on satisfying sexual events, sexual desire, and related distress.

Discussion topic number 2 asks the committee to think about the generalizability of the clinical studies to the population of women who would likely use this product if approved, and then to discuss your level of concern with the risks of hypotension and syncope when flibanserin is used alone and when it's used with alcohol.

This question has several bullets. We'd like to hear what the panelists think on the following topics specifically. One is whether the dedicated alcohol interaction study, which was

conducted mostly in men who are moderate alcohol drinkers, adequately assesses risks in premenopausal women and in those who generally drink less alcohol than moderate drinkers.

We'd like to hear about the feasibility of avoiding alcohol indefinitely while using flibanserin, which is a chronic medication, and taking into account the prevalence of alcohol use in the United States.

We'd like to hear whether the committee thinks alcohol use should be contraindicated in patients using flibanserin, whether a REMS, or a Risk Evaluation and Mitigation Strategy, is necessary and would be able to ensure that the benefits outweigh the risks of hypotension and syncope with flibanserin alone and when it's used with concomitant alcohol.

If committee members think a REMS is appropriate, to comment on what they think of the applicant's proposed REMS, which is a medication guide and communication plan, and whether that's sufficient to ensure safe use or whether additional

elements like restricted distribution elements to ensure safe use, or ETASU -- it's the other name for that -- with pharmacy certification or a pharmacy and provider certification are needed. And there will be a presentation from the risk management folks to help frame some of these questions.

Discussion question 3 asks the committee to take into account the generalizability, again, of the clinical studies to the population who would use it and then to discuss level of concern with any other safety findings. And then we'll end with a voting question, which is a multiple choice question. It asks if the overall benefit/risk profile of flibanserin is acceptable to support approval for hypoactive sexual desire disorder in premenopausal women.

Option A is, yes, with labeling alone to manage the risks. Option B is, yes, but only if certain risk management options are implemented beyond labeling. And Option C is no. We'd like to hear your rationale for your vote.

If you vote for B, which was the option saying additional risk management options are needed beyond labeling, we'd like to hear what specific recommendations you have for these additional options. And if you voted for C, we'd like to hear what additional data you think are needed to ensure a positive benefit/risk profile.

Some have claimed gender bias on the part of FDA when it comes to treatments for female sexual dysfunction and have cited 26 medications approved to treat men with sexual dysfunction and either no medications to treat women with sexual dysfunction or no medications to treat HSDD, so I wanted to take a moment just to clarify the current state of medications approved for treating sexual dysfunction in the United States for both men and women.

Firstly, the 26 medications include about a dozen or so testosterone products, and it's important to note that none of the testosterone products are FDA approved for treating sexual dysfunction in men. They're all approved as

replacement therapy in men who have low testosterone levels and a specific medical condition.

So what is available? Well, women have two classes of medications that are approved for treating pain with intercourse associated with menopause, and men have three classes of medications for their sexual dysfunction, one for Peyronie's disease, which is a condition where a plaque develops under the skin of the penis and causes bothersome curvature. Then men have two classes for erectile dysfunction, which is difficulty achieving and maintaining an erection.

Among the two classes of products approved for women, there are three brand name products, and across the three classes for men, there are nine brand name products.

It's important to note that neither women nor men have FDA approved treatments for other sexual arousal disorders, orgasmic disorders or sexual desire disorders, including the condition we're discussing here today.

So in summary, there are no FDA approved treatments for sexual desire disorders. FDA has, for some time now, recognized that there are women who would benefit from safe and effective treatments. Some claim gender bias on the part of FDA for the current state of affairs. The FDA firmly rejects this assertion.

FDA is always concerned with unmet needs, whether this is in women, men, or in children. But we're still required, even for a treatment that treats an unmet need, to ensure that patients receive more benefit than harm from the treatment.

I'd like to end by saying that we welcome the committee's input on the flibanserin and its challenging benefit/risk assessment, and I look forward to a discussion that's focused today on the science. Thank you.

(Applause.)

DR. LEWIS: Thank you.

Both the FDA and the public believe that a transparent process for information-gathering and decision-making is important. To ensure such

transparency at the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including sponsors' non-employee presenters, to advise the committee of any financial relationships they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcome of the meeting. Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships.

If you chose not to present this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We'll now proceed with the sponsor's presentations.

Industry Presentation - Josephine Torrente

MS. TORRENTE: Thank you, Dr. Lewis, and

good morning. I'm Josephine Torrente, executive vice-president of corporate and regulatory affairs at Sprout Pharmaceuticals. I'd like to take a moment to thank the FDA as well as this joint committee for the opportunity to present our drug, flibanserin, to you today. I'd also like to take a chance to thank the thousands of women who've participated in clinical trials for HSDD over the years.

We've developed flibanserin as a treatment for hypoactive sexual desire disorder, or HSDD, in premenopausal women. Literature estimates suggest that up to 7 percent of the premenopausal U.S. population suffers from this disorder.

This slide is intended to give you a brief overview of key flibanserin features that you'll hear about today. I'll point out that it's a 100-milligram tablet intended for bedtime dosing primarily metabolized by CYP3A4 and also that flibanserin is non-hormonal, working instead through the central nervous system.

Flibanserin benefits from a robust

regulatory history, some of which Dr. Joffe reviewed for us. I won't go through it all but I'll point you to 2010 when a predecessor to this committee reviewed the application.

That review was based largely on two efficacy studies completed at that time, which met one of their co-primary endpoints, a measure of satisfying sexual events. Both studies did not meet the other endpoint, which had been intended to measure sexual desire. Despite that, the previous applicant submitted the application, and the review was denied.

I'd like to now focus you on the more recent history. Three thousand additional patients have been enrolled since that time in 13 clinical studies. These studies were conducted after extensive and helpful discussions with the FDA.

Regarding efficacy, FDA recommended that we conduct a single additional pivotal study with less prohibited medications and showing efficacy concurrently on three endpoints: a measure of satisfying sexual events, a validated measure of

sexual desire, and a validated measure of distress associated with low desire.

Regarding safety, FDA recommended that we complete a phase 3 safety study of concomitant administration with SSRIs and SNRIs and that we complete multiple phase 1 studies including drug-drug interaction studies and importantly a driving study ensuring no next-day impairment based on the bedtime dosing.

This is the entire clinical program, 61 studies in 11,000 patients. Again, we won't have time to discuss them all today. Let me focus you on the 13 new studies I just mentioned.

In the upper right-hand corner, you see the phase 1 studies, including the important new driving study, which did confirm a lack of next-day impairment.

Study 147 is our new study showing safety and efficacy with fewer prohibited medications and showing that efficacy concomitantly across the three new required endpoints. The SSRI/SNRI study confirmed no exacerbation of adverse events from

these products. And we also completed two open-label extension trials.

When we discuss efficacy today, we'll focus primarily on study 147. We'll also refer back to the two previous efficacy trials, studies 71 and 75. When we move to safety, we'll expand to the premenopausal HSDD population, which we call the target population. For less common events, we'll expand further, adding studies in postmenopausal women and the SSRI/SNRI study to have the treated population.

That brings me to our agenda for today. First, I'll ask Dr. Sheryl Kingsberg to come to the podium to discuss HSDD, the unmet need, the impact, and the need for additional therapy.

Dr. Ray Rosen will discuss current modern day instruments available to assess the symptoms of HSDD.

Dr. David Portman will then walk us through efficacy, focused largely on study 147 and on what is the clinical meaning of the efficacy findings we have.

Dr. Stuart Apfel will walk us through flibanserin's well-characterized safety profile. I'll return to discuss our risk management program, and Dr. Portman will close with clinical considerations. All of these experts are available to answer your questions today as are the additional experts listed on this slide, and we do look forward to your questions. And with that, I'd like to invite Dr. Kingsberg to the podium.

Industry Presentation - Sheryl Kingsberg

DR. KINGSBERG: Thank you for the introduction, Josephine, and good morning to all of you. I am a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting. However, as a clinical psychologist specializing in the research and treatment of the women we're discussing today, I have a great professional interest in the result of today's proceedings.

HSDD has been recognized as a medical disorder for almost four decades now, with scores of papers having been published, and they all share

a common theme. This condition has profound implications on women and couples. Yet, despite this wealth of data, the condition is mired in misconceptions.

Now, all of us entered this room today with our own version of what normal sexual desire is. Naturally, that makes us look at desire through the lens of our own experience. But today, we need to look at it through the eyes of these suffering patients.

The stigma that has surrounded them reminds me of the days before anti-depressants when skeptics said depression was all in someone's head. But we learned that treating a neurotransmitter imbalance made a biologic and clinical difference for some of those patients. HSDD should be no different.

So what you see here is a PET scan or neural imaging of the brains of women who report normal desire versus their peers who've been diagnosed with HSDD. Exposed to erotic stimuli, you see a fundamental difference in the deactivation, or

lighting up, of the brain of a woman without HSDD. This blue deactivation, particularly in the prefrontal cortex, signals the brain's quieting, the cooling, to allow for desire to take hold.

The brain of the woman with HSDD does not show the same deactivation. She can't quite access that reward center that triggers the want. Not only do we have this landmark study from 2009, but it's now been repeated multiple times with functional MRI. And again, I draw your attention to the dramatic contrast.

But beyond biology, we know the validity of the condition through the experience of patients. I've heard it for 25 years in practice, so let me describe the prototypical HSDD patient for you.

She is in a stable monogamous relationship. She loves her partner. In fact, she makes a point to tell me that because she wants me to know that it is not because of her partner that she is uninterested.

She used to have a desire that she was happy with, a hunger for sex, but she's lost it, and that

loss has painfully persisted. No longer does she initiate sex or feel receptive to sexual advances. She misses having those spontaneous thoughts or the fantasies that use to indicate innate sex drive. And that drive has been gone for a long time, months and more commonly years by the time, she finds her way to my office.

In the meantime, she's suffered. She's lost a sense of self, a connection with her partner, the benefits of a positive sexual relationship that move from the bedroom to the breakfast table the next morning.

So let me show you that data. In this survey of 306 premenopausal women with low sexual desire, 67 percent of them feel less connected to their partner. There's less communication, and there's a loss of self-confidence. For example, 69 percent reported a negative body image as you see here.

Now, this patient is easily identifiable through the Decreased Sexual Desire Screener. In fact, through it, I rule out things that the HSDD

patient is not. She is not a woman whose lack of desire is due to a bad relationship, or time pressures, fatigue, or a lack of privacy. She is not a woman on the bar scene wanting to boost her appeal with a quick fix.

A woman who has no desire in Baltimore but has desire on vacation on the Bahamas does not have HSDD. Her desire is gone. She wants to want again. And the absence of a single approved medical treatment does not mean that treatment isn't happening today.

She may find her way to my office for psychotherapy, but when the woman's HSDD is due to a biologic cause, the results achieved through psychotherapy alone are often not sufficient. I can refer her to a physician whose only option is to try a medication off-label, bupropion or testosterone most commonly, both which carry risks.

Far too often, what's happening is that these women turn to the internet or in the back of a magazine. They have no other option. In fact, in a study that sought to better understand the

healthcare utilization by women with HSDD, we learned that more than half will turn to the internet or magazine articles.

They're lured by outrageous claims, with some trying these unproven products and procedures. And while they try out of desperation, these do not provide the results the HSDD patient really wants from her treatment. Understanding what the HSDD patient wants from treatment is important because what may be deemed modest by some is meaningful to her.

The following data show you in her own words what she's seeking. She wants to feel normal again. Seventy percent of women say that this is their motivation for seeking therapy.

Over 50 percent emphasized, unsurprisingly, that they didn't want to have the relationship suffer. They love their partners. And over 40 percent of women with HSDD want their femininity back. In fact, the other day, I saw a self-portrait of a woman with HSDD. In it, she had drawn no breasts, no hair, and no hands. That is a

self-image of a woman who is profoundly distressed, a woman who's lost her sense of self.

Today, you will be voting on giving that woman access to a potential treatment, and today, your deliberations will reverberate throughout the field of sexual medicine for years to come. Our next speaker is someone who has made contributions to the field for his entire career. He's a psychometrician that has helped unlock our ability to measure desire, the author of the Female Sexual Function Index, Dr. Ray Rosen.

Industry Presentation - Ray Rosen

DR. ROSEN: Good morning. My name is Raymond Rosen. I'm the chief scientist at New England Research Institutes, and I'm here today as a consultant to the sponsor. I have no financial interest in the outcome of today's meeting.

Efficacy endpoints in the study of sexual dysfunction are always patient-reported outcomes or PROs of one kind or another. Three specific endpoints, one each measuring sexual activity,

distress associated with low desire, and sexual desire itself, provide a complimentary and holistic view of patient benefit in HSDD. I'll briefly review two of these endpoints, and then consider the third endpoint, the FSFI desire domain, in greater detail. Let's start with measuring sexual activity.

Satisfying sexual events. The definition shown on this slide is well-accepted and has been used in numerous clinical trials of female sexual dysfunction to-date. Satisfying sexual events refers to the number of sexual events defined by a variety of sexual behaviors.

SSEs are discrete events that the patient rates as satisfying if she found them gratifying, fulfilling, satisfactory, and/or successful, irrespective of whether the woman achieved an orgasm or not. Events are captured daily by the woman herself in an electronic diary with a maximum of 3 days to record the event.

Next, we have distress, one of the key concepts in HSDD. The female sexual distress scale

is a 13-item PRO that measures sexually-related distress or bother. Specifically, item 13 of the scale asks, "How often did you feel bothered by low desire?" The instrument has a 7-day recall period to assess treatment-related changes.

The Female Sexual Function Index, or FSFI, is currently the most widely used questionnaire for assessing sexual function in women. For full disclosure, I'm the lead author of the FSFI as well as lead author of a comparable questionnaire for men's sexual function, the International Index of Erectile Function or IIEF. The IIEF has been used as the basis for approval of numerous drugs for the treatment of erectile dysfunction in men.

The complete FSFI consists of 19 questions divided into 6 domains. The desire domain is comprised of these two specific questions. Subjects answering these questions have been provided a broad definition of sexual desire, which includes receptivity, thinking about sex, and wanting to have a sexual experience.

It's validated for a 4-week recall period

based on qualitative findings that women experience sexual desire as a state and not as a discrete event. One question assesses frequency by asking, "Over the past 4 weeks, how often do you feel sexual desire or interest?" It's a 5-point scale ranging from almost never or never to almost always or always.

Another question assesses the intensity of desire by asking, "Over the past 4 weeks, how would you rate your level of sexual desire or interest?" also a 5-point scale ranging from very low or none at all to very high.

The FSFI underwent the recommended iterative scale development and validation process that is consistent with the FDA guidelines for PRO development. Today, it's supported by over 300 publications in peer-reviewed journals. Under the umbrella of test reliability, the scale has met or exceeded both test, re-test, and internal consistency standards. Regarding scale validity, both content and construct validity have been established in numerous studies.

Uncertainty about FSFI content validity has been raised in the review of the product before you today. We can briefly address this concern by looking at results of a qualitative validation study conducted by Dr. Denis Revicki.

Very high percentages of pre- and postmenopausal women with HSDD reported that the questions were clear and easy to understand and that the response options provided are appropriate. When asked if the two questions reflect all of their problems with decreased desire, the percentages are somewhat lower.

Let me take a moment to clarify any confusion about this. These lower percentages of agreement could either reflect a need for content changes in the questions or that the patients are considering the consequences or impacts of desire and not the concept of sexual desire itself. It was in fact the latter.

Patients noted the need for additional questions regarding emotional distress, relationship problems, lubrication issues, and

orgasm. This is precisely why qualitative responses on content validity must always be assessed by an experienced psychometrician such as Dr. Revicki.

He reviewed the qualitative feedback and determined the FSFI desire domain was adequate and valid for assessing the concept of sexual desire in women. Other scales or scale domains were included for measuring the broader impact of HSDD, including sexually related distress, bother, and other sexual difficulties. The broad acceptance of this instrument in assessing female sexual dysfunction is further evidence of its fitness for purpose.

Specifically, this past October, 12 of 13 sexual medicine experts on FDA's convened patient-focused drug development panel endorsed the FSFI desire domain as the optimal instrument for assessing sexual desire in clinical trials of HSDD.

This slide summarizes all of the PRO endpoints that are the foundation of today's presentation by the sponsor. You'll find the number of questions, the response ranges, cut

points for clinical meaningfulness, and normative values for volunteers without FSD. Perhaps it can aid in your deliberations today.

I'd like to now introduce Dr. David Portman who will discuss flibanserin's efficacy.

Industry Presentation – David Portman

DR. PORTMAN: Thank you, Dr. Rosen.

I also want to thank the advisory committee, the FDA for giving me the opportunity to present the flibanserin efficacy data. For the record, I'm a consultant to the sponsor, a co-chair of their scientific research committee, but I have no financial interest in the outcome of this meeting.

I am a practicing OBGYN, and I see patients every day just like those described by Dr. Kingsberg. I also conducted several of the flibanserin trials, and through these, I finally had the chance to offer my patients with HSDD a medical treatment option in a clinical trial setting.

We've long understood HSDD, and it's a clear unmet medical need. We have PROs, as discussed by

Dr. Rosen, available that put us in an advantageous position to identify meaningful efficacy.

Today, we'll review some of the clinical trial results as well as exploratory analyses to illustrate the totality of evidence generated in the flibanserin program. The multifaceted nature of HSDD requires that we examine both the individual endpoints and overall patient-reported improvement.

We'll also describe results on a prespecified clinical meaningfulness measure, the Patient Global Impression of Improvement or PGI-I, taking in total a large body of evidence collected since 2002 supports flibanserin's efficacy.

The flibanserin program is extensive and comprehensive. It demonstrated dose response during its development, and the 100-milligram nightly dose at bedtime was identified during the program as the optimal effective and tolerated dose for treating HSDD. And the dose was used exclusively in the new studies.

This presentation will focus primarily on

study 147, as that data is new and was the study requested by the FDA after the initial submission. Consistency between 147 and the previous studies 71 and 75 will be discussed. But before looking specifically at 147, let's review the evolution of the primary efficacy endpoints in the development program.

Studies 71 and 75, the two older studies, succeeded on SSEs but not on the co-primary endpoint of eDiary Desire. Consistent with the recommendations of the FDA and the 2010 advisory committee, the sponsor completed an additional pivotal study, the newer study, study 147. And it showed statistically significant improvements over placebo on the two co-primary measures, SSEs and FSFI desire, and on a key secondary measure of distress associated with low desire, the FSDS-R13. Nominal P values for secondary endpoints in studies 71 and 75 show consistent efficacy.

Now, let's look at the phase 3 study design. All three pivotal studies followed essentially the same design. Study 147 was a 6-month, randomized,

double-blind, placebo-controlled trial in premenopausal women with hypoactive sexual desire disorder evaluating 100 milligrams of flibanserin at bedtime. There were 10 clinical contacts and significant interactions over the 6-month period.

Key inclusion criteria were similar across all the pivotal studies. Patients had to be premenopausal, have a primary diagnosis of generalized acquired hypoactive sexual desire disorder for at least 6 months based on a structured diagnostic interview and DSM-IV criteria.

All women had to be in stable monogamous relationships, and all women enjoyed healthy sex lives before and did not suffer from lifelong low desire. Less stress, a vacation, a romantic dinner, no situation could improve their chronic state of low desire, and they're incredibly bothered and distressed by this change. Their baseline dysfunction is further illustrated by another key inclusion criteria, the validated Sexual Interest and Desire Inventory or SIDI-F.

SIDI-F item 2 determines the level of interest and receptiveness to a partner's sexual approach. To be included in the trial, women had to have a score of zero or 1, seen in the shaded boxes, meaning she always or almost always engaged in sexual activity out of a sense of obligation and never with sexual interest or encouragement.

It's this distressing cognitive distance between desire and behavior that defines HSDD. Every woman enrolled in the trial met this criterion. The average SIDI-F score was 0.5.

Key exclusion criteria are as follows. Potentially confounding sexual disorders were excluded. Active major depression and other confounding general medical conditions were excluded. However, approximately 5 percent of patients had a history of depression, and up to 15 percent had other psychiatric diagnoses.

Medications known to affect sexual function were also excluded. In study 147, the restrictions were loosened to allow to triptans, muscle relaxants, and other drugs not allowed in

studies 71 and 75. These criteria yielded the following patient demographics: an average of 36 years of age; 75 percent of the participants were white, both of which mirror the population of premenopausal women suffering from HSDD as defined by epidemiological surveys. No differences were observed at baseline between placebo and the flibanserin groups.

Key baseline characteristics on the enrollment population are these. Their average time in a stable monogamous relationship was over 10 years. Their symptoms of HSDD had been present for 4 to 5 years, almost half of their relationship. At baseline, patients had on average 2.5 SSEs, so 1 every other week on average. Over 50 percent had 2 or less per month, and 22 percent had zero at baseline.

The FSFI desire score was 1.9 at baseline, well below the cutoff score of 3, and the FSDS-R13, which measures distress about low desire, was 3.4 out of 4, meaning that they were almost always bothered by their low level of desire.

Baseline scores on all instruments in all trials were very consistent and in the significantly affected range. There were not meaningful differences at baseline between the flibanserin and the placebo groups.

Over 75 percent of the patients completed the study. Similar to other CNS therapies, higher numbers of flibanserin patients discontinued versus placebo, 24.7 versus 18.2.

Given the original protocol-specified LOCF imputation rules employed for these data, the sponsor conducted numerous sensitivity analyses, which confirmed robust study results despite these dropouts. And our statisticians are here to answer any questions.

I will be presenting the prespecified analysis endpoints for 147. The primary endpoint was mean change in the number of SSEs from baseline through 24 weeks. There's a steady separation from placebo as early as 4 weeks for SSEs.

The descriptive nominal separation between flibanserin shown in green and placebo shown in

gray was achieved at all time points. And for this co-primary endpoint at 24 weeks, high statistical significance was reached. The absolute mean difference was 1.1 SSEs, and this has been recognized as clinically meaningful to patients suffering with HSDD.

Another way to understand this efficacy is to take the patients perspective. Flibanserin-treated patients entered the study having on average 2.5 SSEs per month. In 24 weeks, they doubled their number of events from 2.5 to 5.

We can also look at how flibanserin affected desire with FSFI. FSFI desire was chosen as the co-primary endpoint in study 147 replacing eDiary Desire. The FSFI desire domain measures an entire range of results. The goal of therapy is targeted to the moderate range of effect.

Flibanserin is not designed, nor capable, of inducing extremes of hypersexuality. It's aimed at rebalancing an acquired discrepancy in satiety and excitatory signals in the brain and restoring the patient's previous levels of desire. As with SSEs,

we see very early separation from placebo, and the prespecified endpoint at 24 weeks was highly statistically significant with a mean change of 0.3. Looking at the clinical meaning of this magnitude of change is important, and we'll put that into context in a moment.

But before that, let's look at the third key endpoint, which a defining characteristic of HSDD, distress. Distress about low desire was measured using the female distress scale. Distress or bother is what typically motivates the patient to seek treatment for HSDD.

As with SSEs and FSFI desire, there's early separation from placebo by 4 weeks and again at every single time point nominal separation from placebo. And at the prespecified endpoint of 24 weeks, the difference from placebo was minus 0.3, a highly statistically significant result.

Perhaps most striking is how efficacy is reproduced across all three pivotal trials. We see consistent results for all these key measures across studies 147, 71 and 75. Please note the

p-values for desires and distress are nominal for studies 71 and 75.

The multidimensional improvement shown here reflects meaningful efficacy for HSDD patients. Global sexual function improvements with a focus of secondary endpoints inform the clinical meaningfulness of flibanserin treatment.

The PGI-I is a global question with face validity that asks how has your condition, low desire, and being bothered by it improved during the study, with a range from 1, very much improved, to 7, very much worse. A PGI-I responder can be defined as scoring 3 or better.

Fifty-two percent of patients reported improvement on flibanserin compared to only 38 percent on placebo for an absolute difference of 14.1 percent or a relative 26 percent greater response on treatment.

This classic U-shape distribution supports a true drug effect over placebo with responders on flibanserin gathering on the right, indicating improvement, while placebo tend to cluster on the

left, indicating no change or worsening. Using PGI-I data, we can also determine a responder threshold for each key efficacy endpoint.

Here, you see the calculated prespecified thresholds for clinically meaningful response. The difference between improvement and no improvement on PGI-I anchored to three main efficacy endpoints for study 147.

In this case, you see the responder threshold anchored to FSFI desire, the prespecified analysis agreed to with the FDA. The same analysis was then applied to SSEs. And lastly, the key secondary endpoint threshold for FSDS.

Using these prespecified thresholds, clinically meaningful improvement with flibanserin compared to placebo was seen. A relative 20 to 25 percent greater number of flibanserin patients met this responder definition for all three anchored endpoints. The results were highly significant. By 24 weeks, 46 to 60 percent had significant benefit from flibanserin when applying this responder analysis. The FDA's ROC responder

analysis yielded very similar results.

More stringent cut points can also be applied to look for even greater levels of response. Here, you see highlighted cut points beginning at one SSE, FSFI desire of 0.6, FSDS of minus 0.5 in the center of these three cumulative distribution charts.

Higher cut points of response are seen to the right. Even with more stringent responder definitions, responders are always much more likely to be on flibanserin compared to placebo. For example, look at patients with an increase in 4 or more SSEs per month from baseline, 1 more per week, in the far right column of the SSE graph. Patients on flibanserin were nearly twice as likely to have this level of response compared to placebo.

Two final endpoints to illustrate the clinical meaning and totality of flibanserin efficacy or the total FSFI scores and the FSDS-R, the FSFI total is composed of 6 domains: arousal, lubrication, orgasm, satisfaction, desire, the absence of pain. The total score, seen to the

left, increased on flibanserin again as early as 4 weeks, and by 24 weeks achieved a highly significant p-value.

Importantly, all relevant subdomains, seen on the right, improved. Not only desire but many other critical aspects of overall sexual function improved in these women as well.

Total sexual-related distress scores also improved and are highly significant at 24 weeks. This demonstrates positive impact on many different aspects of distress such as guilt, inferiority, and embarrassment, the essence of HSDD and its impact on quality of life. Taken together, flibanserin shows a consistent picture.

Three main endpoints across all of the phase 3 studies mirror one another. The shape of these curves are consistent, and they tend to separate and achieve significance by roughly 12 weeks and persist out to 24 weeks.

This observation led the label recommendation that non-responders at 12 weeks consider discontinuing therapy to conclude the

efficacy. Flibanserin was proven effective for women with longstanding, generalized, acquired HSDD.

Efficacy was demonstrated across the three prespecified endpoints in a new more inclusive pivotal trial. These validated measures of desire, distress, and activity were endorsed at last October's workshop. Looking at these endpoints in the earlier pivotal studies, we see the same improvement over placebo.

Parallel improvements in total FSFI scores and its subdomain indicate that improvement extends beyond desire to many aspects of sexual function including arousal, orgasm, and satisfaction.

Sexually-related distress overall was also significantly reduced. And a responder analysis demonstrated benefit at increasingly rigorous PGI-I anchored thresholds. Within 6 months, 46 to 60 percent of women with longstanding HSDD received meaningful benefit from flibanserin.

All these findings support the efficacy of flibanserin as a novel, non-hormonal treatment for

HSDD. And now, for safety, here is Dr. Stuart Apfel.

Industry Presentation - Stuart Apfel

DR. APFEL: Thank you, Dr. Portman.

My name is Stuart Apfel. I serve as vice president of safety for the sponsor. I'm also an associate professor of neurology at the Albert Einstein College of Medicine in New York.

Flibanserin is a CNS-acting drug. It is a post-synaptic, serotonin 5-HT1A receptor agonist and 5-HT2A receptor antagonist that preferentially binds to neurons, expressing these receptors in the prefrontal cortex of the brain. These neurons serve to exercise inhibitory control over subcortical reward centers.

Although the precise mechanism of action of flibanserin is not known, it is believed that flibanserin causes a decrease in inhibitory serotonin activity and an increase in excitatory dopamine and noradrenergic activity.

These changes are believed to restore a balanced control over the brain's reward centers to

the prefrontal cortex, enabling women with HSDD to experience sexual desire when appropriate. As with most CNS acting drugs, flibanserin has other CNS effects as well, and these relate to its safety profile.

In this presentation, I will summarize the general adverse event profile and then focus on adverse events of special interest that emerged from flibanserin's CNS effects.

About 3,000 premenopausal women with HSDD were treated at the proposed 100 milligrams nightly therapeutic dose. Adding the postmenopausal population brings the number to almost 4,000 women treated with 100 milligrams of flibanserin. In the largest all exposed population, which includes anyone in any study who received flibanserin, 8,500 patients were exposed to flibanserin.

More than 1800 subjects received the proposed 100-milligram qhs dose for greater than 6 months. Eight hundred and fifty were treated at this dose for more than a year, and about 90 for more than one-and-a-half years.

Most of the data I will present comes from the target population data set. This data set represents the target patient population for whom flibanserin is being developed. It pools five 24-week, phase 3 studies in the intended population of premenopausal women with HSDD. This pool includes the trio of pivotal studies Dr. Portman described when presenting the efficacy data supplemented by a supportive phase 3 study conducted in Europe and another one that assessed alternate doses of flibanserin.

To better understand events that occur infrequently, we'll also look at the larger treated population set.

This adds to the target set three other supportive phase 3 studies, one study that looked at flibanserin use with SSRI and SNRIs in premenopausal women with HSDD, and two that were conducted in postmenopausal women with HSDD.

The frequency and characteristics of the common adverse events in the adverse events of interest were highly similar between the target and

treated population sets. To detect rare events, we'll expand further to the all-exposed set that includes 8,583 participants that received flibanserin at any dose in 61 clinical trials.

The target population is larger than the efficacy population that Dr. Portman showed you, but the demographic profile is essentially the same and, again, well-balanced between placebo- and the flibanserin-dosed groups in terms of age, race, and BMI.

Two-thirds of patients exposed to flibanserin experienced adverse events in the target population compared with 56 percent of the subjects who received placebo. The vast majority of these adverse events were mild to moderate in severity. Severe events were infrequent as were SAEs, which were more common in patients receiving flibanserin.

There was 1 death in the target population, a patient on placebo who died in a plane crash. Treatment was generally well-tolerated with about 13 percent of subjects on flibanserin discontinuing

because of adverse events compared with about 6 percent of patients on placebo.

The most common adverse events observed in the program, defined here as those that occurred in at least 2 percent of subjects receiving flibanserin and also occurring at least twice as often as in the placebo-treated group, was similar to those of other active CNS drugs such as paroxetine, duloxetine, and bupropion.

Sedation-related adverse events such as dizziness, somnolence, and fatigue were as a group the most frequent events. Nausea was also seen commonly. The most common adverse events were also the most frequent events that led to treatment discontinuation.

I will examine in greater detail two sets of CNS-related adverse events that are of particular interest. These include sedation-related events as well as hypotension and syncope-related events. While discussing these events, I will pay particular attention to the impact of CYP3A4 inhibitors and alcohol on these events. I'll start

first with sedation.

This slide summarizes the frequency of the four major sedation-related adverse events in the target population set of premenopausal women with HSDD. Looking left to right across the individual terms as well as the totals at the bottom, a dose response pattern becomes apparent.

Sedation-related events typically start during the first week or two of treatment as would be expected of any common adverse event. This slide summarizes the duration of the sedation-related events as derived from adverse event reporting.

The median duration of the common sedation-related adverse events, again, dizziness, somnolence and fatigue, were very similar between the 100-milligram qhs-treated group and those receiving placebo, ranging from 10 days to about 1 month in duration. This does not mean that patients experience sedation-related events continuously for that time. In fact, phase 1 data, where subjects were in-house and more precise

duration could be recorded, shows that most sedation-related adverse events lasted for less than 5 or 6 hours.

Rather, the events were episodic and the long durations recorded was likely an odd effect of the way adverse events are generally recorded during phase 3 trials.

These results support bedtime dosing to minimize the impact of sedation. As you can see here, the incidence of each sedation-related adverse event increases as the doses get higher with the exception of the 50-milligram bid dose with respect to the 100-milligram qhs dose, where sedation appears reduced when flibanserin 100 milligrams is dosed at bedtime.

What happens when flibanserin levels are pushed even higher? Increased exposure to inhibition of flibanserin metabolism through co-administration of CYP3A4 inhibitors increases the incidence of some sedation-related adverse events although not all. Although the incidence of sedation-related adverse events increased, there

was no increase in severe sedation-related adverse events or SAEs.

The other drug interaction of concern is co-administration of a CNS depressant such as alcohol. We do not have continuous alcohol use data in our phase 3 program although alcohol use was permitted in the phase 3 studies. About 60 percent of participants identified themselves as casual drinkers.

We compared the incidence of sedation-related adverse events in patients who reported alcohol use and those who did not. Being an alcohol user results in a 9.5 percent increase in the rate of adverse events overall with flibanserin use versus a 4.3 percent increase in the placebo group.

To more thoroughly understand the impact of alcohol use with flibanserin on safety, we conducted a dedicated crossover Alcohol Challenge Study. Challenge studies look at drug effects under extreme conditions.

In our alcohol challenge study, subjects

took their flibanserin in the morning, which we've already noted can exacerbate sedation, and then they had to consume either 0.4 grams per kilogram or 0.8 grams per kilogram of ethanol within 10 minutes on a nearly empty stomach. As you can see, the incidence of sedation-related events increases in both flibanserin concomitant use groups.

The vast majority of the sedation-related events in the alcohol challenge study were mild or moderate in severity. Even the combination of flibanserin with the high dose of 0.8 grams per kilogram ethanol resulted in only 3 sedation-related events that were considered severe.

It is anticipated that the impact of these events would be mitigated by nighttime dosing. To manage these effects, our proposed labeling advises patients to avoid alcohol until they know how flibanserin affects them.

Although in phase 3, alcohol users had more sedation-related adverse events than non-users. Again, the severity of these events were, for the

most part, mild or moderate with relatively few severe events. Our proposed label warns about CNS depression and the risk associated with alcohol use.

Sedation is an important and common adverse event associated with flibanserin. It is usually mild and short-lived, and we believe it can be managed effectively with nighttime dosing. Sedation-related events are common adverse events with CNS active drugs as illustrated by this slide.

The numbers here represent the incidence of somnolence, dizziness, and fatigue reported in the package inserts of other CNS-active drugs. Flibanserin is comparable or better than most. Take particular note of the rather high incidence of these adverse events reported with bupropion or Wellbutrin, a drug again that is currently being used off-label to treat HSDD.

We've also taken a close look at adverse events related to hypotension and syncope, which the FDA correctly notes is the most concerning event in the flibanserin program. Looking across

the entire program, hypotensive and syncope-related events are frequent when flibanserin is used in combination with CYP3A4 inhibitors that increase flibanserin exposure. Events are also common when flibanserin is dosed in the morning with rapid alcohol consumption. Let's take a closer look at these events.

Three events occurred when flibanserin was administered with fluconazole. Fluconazole was administered as a 400-milligram loading dose followed by 3 days of 200 milligrams before the 5th day when it was administered together with 100 milligrams flibanserin.

In this study, we saw a mean 7-fold increase in AUC and a mean 2.2-fold increase in the Cmax. The 3 subjects, with by far the highest elevations of Cmax, each experienced hypotension-related adverse events. One of them had a more significant episode than the other two. Her blood pressure dropped to 64 over 41. She was sent to the emergency room, and then recovered after about 3 hours and returned to the clinic. Each of these

subjects went on to complete the study.

The last event listed occurred when flibanserin was studied with ketoconazole, a strong CYP3A4 inhibitor that increased the AUC 4.5 fold and the Cmax almost 2 fold. In this study, a single subject who took ketoconazole and flibanserin experienced a significant hypotensive event leading to syncope during the treatment period.

Interestingly, the same subject experienced a similar episode of hypotension and syncope about 17 days after treatment was completed. In view of the time period, the investigator felt that that event was unlikely to be related to study medication.

Although these events are seen in only two of the eight high-exposure studies, they reinforce the contraindication of flibanserin use with strong or moderate inhibitors.

These six events occurred in the Alcohol Challenge Study I described earlier. Each of these six events completed the study following the event.

Again, our proposed label will warn about the risks of CNS depression, hypotension, and syncope if alcohol was taken together with flibanserin.

While we fully agree with the FDA concerns regarding the risk of hypotension and syncope when flibanserin is taken with high doses of CYP3A4 inhibitors or CNS depressants like alcohol, we firmly believe that the risk is far lower, and the real-world user is represented by the large phase 3 population.

We found a total of 16 events in nearly 4,000 patients in the phase 3 program when using a broad definition of hypotension and syncope. In phase 1 studies, flibanserin was given alone to 1,235 subjects almost always in the morning. We saw 6 events, and 2 of those subjects had high exposures. Let's take a closer look at these events.

To analyze hypotension and syncope-related adverse events in the phase 3 program, we looked at any preferred term that could possibly be associated with hypotension or syncope. Few

adverse events related to hypotension or syncope were reported in the phase 3 clinical program, and the low rates were similar across treatment groups including placebo suggesting that there is little increased risk for these events when flibanserin is used as indicated.

In addition, only a few of the patients with hypotension or syncope-related adverse events discontinued from the study suggesting that the occasional events seen were likely to be tolerable.

All of the phase 1 patients who experienced hypotension or syncope were dosed during the daytime. This slide briefly summarizes the 6 subjects who experienced syncope-like events or hypotension on flibanserin alone in the 38 phase 1 clinical studies.

A few comments. The subject number 13 in the paroxetine study, the investigator judged the event to be unrelated to the study drug since it occurred long after single dose drug administration. Three of these subjects completed the study despite their event. The subject in the

Human Abuse Liability Study received 200 milligrams, a 2-fold supratherapeutic dose of flibanserin.

Hypotension and syncope are sometimes seen for wide variety of CNS active drugs. This table was generated from the package inserts from similar CNS-active agents. A description of "frequent" would indicate that the event occurred in greater than 1 percent of the studied population. "Infrequent" would indicate that the event occurred between 0.1 percent and 1 percent of the study population.

As you can see, flibanserin is comparable to most of these CNS active drugs with the exception of citalopram and bupropion, while hypotension and syncope occurs much more frequently. Again, remember that currently, bupropion is commonly used off-label to treat HSDD.

To fully assess the potential impact of sedation and hypotension-related events, we must also examine whether or not they increase the risk of other adverse events such as accidental

injuries, so we looked across the target data set to analyze the incidence of accidental injury and road traffic accidents.

For road traffic accidents, the number of events are too small to draw any conclusion. The frequency of the accidental injuries in general was similar between subjects that received flibanserin and those that received placebo.

We then evaluated accidents that were temporally related to sedation-related adverse events. At the suggestion of the FDA, we included the following events as being sedation-related: dizziness, somnolence, fatigue, hypotension, circulatory collapse, and sedation.

As you can see, the data appears to show that flibanserin 100-milligram dosing results in 3 times the percentage of accidents reported in the placebo group. However, the numbers are very low, 4 events in the placebo group and 10 in the flibanserin-treated group.

Adding the postmenopausal population slightly increases the number of accidents reported

but reduces the ratio between flibanserin 100 milligrams and placebo from 3 to 1 to 2 to 1, highlighting the small number of events observed.

To further investigate the relationship between flibanserin use and accidents, we conducted a dedicated driving study developed in collaboration with the FDA. It was designed to evaluate the next-day residual sedative effect following nighttime dosing of flibanserin acutely in that steady state and including a supratherapeutic dose.

This crossover study used both a placebo and an active control, the hypnotic drug zopiclone 7.5 milligrams. Zopiclone was chosen as the active control because it has been shown in numerous other studies to significantly impair driving performance.

Driving and cognition assessments were done at two time points, on the morning following the first dose of study drug and on the morning following the seventh dose. The primary endpoint was the SDLP or Standard Deviation of Lateral

Position.

SDLP is a measure of variability in lane position used to characterize the effect of sedating drugs on weaving in traffic as illustrated by the figure on the left.

On the right is a graphical representation of the study results. The X-axis shows the change in SDLP. A solid vertical line at zero represents the subjects' performance on placebo. Higher scores to the right of the zero line represent an increase in weaving compared to placebo. Lower scores to the left of the zero line indicate better driving performance compared to placebo.

The blue triangles on the right represent the zopiclone group, and as expected, the zopiclone group did significantly worse than placebo. The green circles and square depict the two flibanserin dose groups, 100 and 200 milligrams. Both doses were non-inferior to the placebo-treated group.

The horizontal lines in the whisker plot represent confidence intervals, not variability, so any line not touching the vertical zero line

indicates statistically significant differences from placebo.

Twelve secondary outcome measures were included in the dedicated driving study, and the results are represented in greater detail in the briefing book, but the bottom line is summarized here. None showed any evidence of impaired of driving performance with either acute or a steady state administration of flibanserin at the 100- and 200-milligram dose. There was also no evidence of impaired cognitive performance with flibanserin administration on the cognitive measures.

As you have seen, our knowledge of flibanserin safety is derived from over 8,500 subjects, over 1,000 of which were exposed for at least 1 year. The most common adverse events were dizziness, somnolence, and nausea, and for the vast majority of the time, they were mild in severity.

Sedation-related adverse events are characteristic of the flibanserin safety profile. They are relatively frequent events but were not

associated with an increased risk for driving impairment as confirmed by a dedicated driving study. Overall, nighttime dosing helps mitigate the effect of sedation-related adverse events.

Hypotension and syncope were infrequent events, usually reported in patients with daytime dosing, markedly increased flibanserin exposure, or when flibanserin was combined with a CNS depressant such as alcohol. Thank you.

I'll call Josephine Torrente back up to discuss risk management.

Industry Presentation - Josephine Torrente

MS. TORRENTE: Thank you to Drs. Portman and Apfel for walking us through the flibanserin data. As Dr. Apfel showed, flibanserin is very well characterized, and when taken appropriately is well-tolerated. We've developed a risk management program that is comprehensive and is designed to ensure appropriate use through intensive communication and focused collection of postmarketing activities.

The program is based on a foundation of

four key communication efforts: the package insert, a REMS, enhanced pharmacovigilance, and a staged launch. Each of these creates consistency and repetition of messages, builds awareness regarding adverse events, patient selection, and the avoidance of increased risks.

The key messages being communicated are the need for bedtime dosing, the importance of avoiding CYP3A4 inhibition, the potential effects of concomitant alcohol use, and the importance of prescribing flibanserin only to those patients who are appropriate.

In developing this program, we considered how much risk management was appropriate in light of other drugs for non-life threatening diseases. When we looked at drugs with a significant sedation potential and another, more significant adverse event that was less frequent, we often saw no REMS. You'll note that one of your voting questions asks whether flibanserin should be added to this category.

When we looked at drugs with more serious

adverse events such as MACE or anaphylaxis, we found communication plans or medication guide-only REMS, and we put flibanserin in this category.

Elements to Assure Safe Use, or ETASU, including those with prescriber or pharmacist certification, appeared reserved for life-threatening risks with catastrophic outcomes. We do not believe this is appropriate for flibanserin.

So let me walk you through our proposed risk management program. It begins of course with a package insert. You've heard some of the contraindications and warnings. In addition, there's a limitation on use advising that flibanserin is not approved for any other form of female sexual dysfunction. And as Dr. Portman mentioned, there is a recommendation to discontinue therapy after 12 weeks for non-responders, limiting the number of patients who will be exposed to flibanserin after that time.

The REMS itself includes a medication guide as well as Dear Health Care Provider and Dear

Pharmacist letters, which will also be given to professional societies. There are HSDD-specific tools such as the decreased sexual desire screener and two flibanserin-specific tools, the appropriate use checklist and patient counseling checklist intended to aid physicians in appropriately prescribing flibanserin. There is also of course a flibanserin website and a REMS website.

The REMS will be assessed. We will use primary data sources that are traditional: in-depth interviews, knowledge, attitude and behavior surveys, as well as patient surveys. But we also intend to mine secondary data sources to understand how flibanserin is being used.

We'll look for indications of patient age, whether bedtime dosing was in fact recommended, whether the med guide was dispensed, what concomitant medications were used, and whether patients did in fact discontinue.

Our enhanced pharmacovigilance program is intended to collect in-depth follow-up of events of special interest with a focused questionnaire,

which will allow us to collect details such as timing of dosing in relation to the event and, importantly, risk factors such as whether alcohol use was involved. All of these efforts are intended to allow us to continually assess and improve the REMS.

The last pillar is a staged launch in which we commit to no direct-to-consumer broadcast advertising of flibanserin for 18 months. This is intended to provide ample time for physicians to gain experience with the drug and learn from our healthcare provider-directed communication efforts prior to any patient demand.

It's in this context that we present flibanserin to you. And I'd now like to ask Dr. Portman to close our presentation with clinical considerations.

Industry Presentation - David Portman

DR. PORTMAN: Flibanserin has demonstrated the ability to improve desire, reduce the stress, and increase satisfying sexual events in premenopausal women with HSDD. These benefits are meaningful to women with HSDD, and by

patient-reported outcomes and their own global impression of improvement, they told us that. And they echo the voices of the many patients that spoke in this very room at the October 2014 patient-focused drug development meeting hosted by the FDA.

What the patients said that day was that they wanted to try to regain the healthy sexual life they once knew and the sense of self-worth that came from being sexually alive. And that's what flibanserin does.

The FSFI desire domain, our co-primary endpoint in 147, asks about the frequency and intensity of sexual desire. Always feeling very high levels of desire is not the appropriate or sought-after goal of treatment for HSDD.

Women in the flibanserin clinical program started with absent or very low levels of desire, and with treatment went to sometimes having moderate desire, and responders approached moderate to high desire some time to most of the time.

The stress also goes down from almost always

to occasionally. This type of result that starts to bring them back toward their normal would be a most welcome treatment for my patients. And my patients with HSDD are very much like the women in the trials and were in the trials. They're in long-term committed relationships and have had the condition for some time. Remember, it was 10 years in a relationship, half the time with HSDD, 43 to 60 percent of them had a significant benefit from flibanserin treatment.

That affords a woman with HSDD who has lost the desire, intimacy, happiness, and self-fulfillment, once a part of her sex life, to begin to feel more like herself again with less dissonance and distress. By the numbers, we saw consistent results across all pivotal studies. For the patient, this confirms a true and meaningful treatment effect and improvement in overall global sexual function.

Efficacy must be balanced with safety. The most common side effects are dizziness, somnolence, nausea, and fatigue, but mild and largely mitigated

by bedtime dosing and responsible use. The sedation-related AEs do not cause cognition or driving impairment the next day. I'll certainly reinforce the importance of bedtime dosing to my patients.

Further, hypotension and syncope occur infrequently and are of concern mostly in the presence of high exposure such as significant CYP3A4 inhibition or with significant alcohol consumption.

My colleagues and I will counsel our patients about flibanserin's potential to cause sedation, its interaction with CYP3A4 inhibitors and alcohol, just as we do with our patients commonly prescribed SSRIs, CNS medications, micronized progesterone, and the like.

I'd also like to make sure that my patients understand that in order to continue on this therapy, they'll require follow-up, assessment for response, which should be seen by 12 weeks, and be monitored appropriately for side effects and adverse events. I believe my patients will

understand the benefits and risks and comply with the instructions to obtain the improvement demonstrated with flibanserin.

We've seen a lot of numbers today, but beyond those numbers, there's a clinical perspective. As an OBGYN, I've prescribed my patients their contraception; I talk to them about safe sex, delivered their babies, and spoken to them about their most intimate concerns. And when something is not working for them sexually, often it's their distressing lack of sexual desire.

Now, no one pill is ever going to solve every sexual problem for every patient, male or female, with sexual concerns. Along with my colleagues in every community as informed healthcare providers, we share decision-making with our patients, discussing expected benefits and risks of all therapies, and prescribing flibanserin will be no different.

Let's at last begin to address this significant unmet medical need by turning the treatment decision over to women suffering with

HSDD and their healthcare providers. Thank you.

(Applause.)

Clarifying Questions to Industry

DR. LEWIS: Thank you. We'd like to take questions for the sponsor. I'll ask you to raise your hands so that we can manage the flow.

Dr. Guess -- I'm sorry. Dr. Phillips?

MS. PHILLIPS: Several of the speakers commented on the large placebo response that was seen and also noted that there were a lot of clinical contacts during -- in the course of the trial, for example, 10 visits within 6 six months.

Could you comment on the impact of the provider-patient interaction as part of the trials and the impact that might've had?

So for example, which percentage of the patients in your clinical trials had had psychotherapy prior to and which ones initiated or continued psychotherapy or other kinds of interactions during the trials and how that might have impacted the results?

MS. TORRENTE: Sure. I think we can address

the placebo response generally first, and then I think we can pull up some data on who had prior behavioral therapy in the trials.

I think first, I'd like to ask Dr. Portman if he would address the placebo response generally.

DR. PORTMAN: You're correct in recognizing the large placebo response in this trial. It is not unusual in female sexual function studies to see this kind of placebo response, nor is it unusual to see this kind of placebo response in many patient-reported outcome studies, whether it be pain, vasomotor symptoms, or overactive bladder.

So we know that when there is cortical top-down input and there's a lot of clinical contacts, as you mentioned, there is a form of behavior modification. These are patients who are filling out diaries. There's an incentive to participate.

In fact, patients in the study often who had zero sexual events were asked and obligated to have one event. So by definition, that clinical contact and the study participation really does create a

rarefied environment that is prone to having large placebo response.

Again, I think it's helpful to see a comparison with effect size. I think that the challenge when we look at placebo responders is what's the true drug effect. I think the response from baseline is very impressive. And whenever you can demonstrate a drug effect with a very robust placebo response, you've met a very high bar.

So for instance, something that's very familiar to this division are the overactive bladder drugs, and most recently approved was mirabegron or Myrbetriq. If you look at their co-primary endpoints, there were 1.5 fewer incontinence episodes, but compared to placebo-corrected, it was only a half an episode.

Similar rates on micturition. The responder analysis, again, because of the high placebo response rate, even though there was a response in 70 percent of the patients, placebo-corrected, it's only a 10 per set differential.

Again, this is a biologic condition just as

HSDD is, and the modifications and the clinical encounters, diary-keeping, certainly create a placebo response, something that we're not unfamiliar with in this class of drugs.

MS. TORRENTE: I wonder if I can ask the team if we do have data on prior behavioral therapy. I know that it was not high.

So it was an exclusion criteria in the study to have had behavioral therapy within 12 weeks of baseline. Seventeen to 29 subjects had prior behavioral therapy in the study, so very, very low out of thousands of patients; so too few for us really to make any conclusions.

DR. LEWIS: Thank you.

Dr. Gerhard? And if you can, try to direct your question to a specific presenter.

DR. GERHARD: Hi. This is Toby Gerhard. Just two clarification questions. It's under the heading clinical meaningfulness. I don't recall exactly the presenter. It's slide 52 and 53.

For slide 52, the PGI-I, the grouping seems a little confusing as worsened includes much worse

and very much worse, but improved includes minimally improved, much improved, and very much improved. Do you have the breakdown for all seven categories of the actual scale?

That's question 1. And question 2, just to the next slide, 53, the denominators for the placebo and the treatment groups are quite a bit smaller. It looks a bit differentially smaller than the actual number of people in the trial, which, if I looked this up correctly, are 545 and 542.

Could you clarify who the people that weren't included in these numbers are?

MS. TORRENTE: Sure. Maybe I'll handle the second one first as I think that's quicker. So this is the week 24 data, and there was some dropout during the study, so these numbers represent week 24, patients who arrived. There are no exclusions of patients who met week 24.

If we can go back to your other slide, the PGI-I has 7 points, you're right, so it is an imbalanced instrument in and of itself. I know

that we do have the breakdown by every category. I'm not sure we have that slide with us. I don't think we do. We may be able to pull that up at the break for you and give it to you.

DR. LEWIS: Thank you. Dr. Lincoff?

DR. LINCOFF: Could you please show us slide 61, CC-61? It's on page 31 of our books. And this is probably directed to Dr. Portman.

MS. TORRENTE: Could we go to slide 60, please?

DR. LINCOFF: Well, actually -- 61.

MS. TORRENTE: Sixty-one without the build.

DR. LINCOFF: Yes, or with the build.

MS. TORRENTE: Okay.

DR. LINCOFF: Because it relates to the build. So I agree that a key part of any kind of risk management is to discontinue the drug in non-responders, then you're focusing the risk or you're allowing the risk to occur in the patients who are getting the benefit.

The problem is that with a placebo response rate like this, the magnitude of placebo response

is substantially more than the magnitude -- the difference between the active drug and the placebo. So how do you really expect to differentiate those who are responders to the drug per se given this sort of placebo response rate?

MS. TORRENTE: I think that's a clinical judgment, and this is not intended to tell patients to come off at 12 weeks. It's intended to have them have a visit with their physician. Again, we'd call Dr. Portman as to how he would make that decision with his patient.

DR. PORTMAN: In clinical practice, we're not going to have the luxury of having a delta between placebo and active treatment, but we also don't have that rarefied environment where there's all those interactions, which I do think do drive significantly the placebo response.

Whether or not a study that was a wait list type of study, where all they did was come in and then come in at the end of the 12 weeks and didn't get all the encounters, we would see a much different delta. That study is yet to be done.

But I think that the way that we ask patients about meaningful response, especially with the PROs and the PGI-I, is asking them in their own words, are you getting improvement, are you feeling better?

I think that when the patient -- and when we put that in the context of any sedation-related or some of the more common related adverse events, that clinical decision is one that we make every day with every treatment that we have, even those that do have significant placebo responses. And I think that that's going to be readily apparent to most clinicians who know their patients, and they'll identify that meaningful response.

So I hope that in the clinical setting, in the community setting, we're going to see the true treatment effect, and that's going to be something that the clinician and the patient can base their decision to continue treatment on.

DR. LEWIS: Dr. Gellad?

DR. GELLAD: Thank you. Yes, I had two questions, actually for Dr. Rosen -- for both of

you actually. The first question was about the length of treatment.

What is the assumption about how long individuals will be on this treatment and if that's been thought about at all, because there were very few clinical trials who were on treatment for more than a year and a half.

The second question is just clarification about direct-to-consumer advertising. It sounded like it was specific to broadcast, but I assume then that means print and samples are still going to go forward, just as clarification. Thank you.

MS. TORRENTE: Let me answer the second one since I can handle that one on my own. There's been no sampling plan that's been developed yet, and that's still on the table whether we even would do sampling. As to broadcast, certainly, we've committed to no broadcast television and radio. Whether print advertising would be in less than 18 months, whether that would go out in 12 months, we haven't gotten to those details.

If that's an important thing that the

committee is interested in, we'd be happy to hear your feedback on that and the importance of that. We saw the broadcast ads as really the ones that had the most impact, and that's where we focused. But those plans obviously can change.

In terms of your question on the length of therapy, you're right that these were six-month studies as is typical for chronic treatments. I think discontinuing at week 12 for no response is our typical view of when patients would come off. For patients with benefit, I think this is symptomatic therapy, and it would be again a clinical judgment.

I feel bad for having Dr. Portman get up and down so many times, but I wonder if he could help us with how a clinician would decide how long to keep a patient on.

DR. PORTMAN: I'm getting my exercise this morning. So HSDD, as far as our understanding, is a chronic condition, maybe remitting. And then in that way, it may mirror some other CNS types of conditions.

So for instance for depression, major depression where you do have patients on long-term SSRI therapy, there are patients who undergo a trial off therapy if they have recurrence. We know that those are the patients who may be on long-term indefinite therapy.

I think that that model may be suitable here. We obviously will need more information, hopefully post-approval, to see how patients are doing long term to make sure that efficacy -- although the open label studies did show persistence of effects, patients' circumstances change.

Although the patients that we studied have generalized acquired HSDD, which means that usually no situation does change it. But if perhaps this medical treatment helps them incorporate certain communication and behavioral strategies that then allow their own spontaneous desire to perhaps change the imaging that we saw that Dr. Kingsberg brought up, maybe we would see that kind of remission, and that patient might benefit from a

trial off therapy. She would certainly know if her symptoms recur and they become distressing to her.

DR. LEWIS: Thank you. Dr. Curtis?

DR. CURTIS: Thank you. So about 40 percent of the participants in your trials were also using hormonal contraception, and so I was wondering if you could comment a little bit on the safety data for that.

Hormonal contraception, at least combined oral contraceptives, are usually considered a weak CYP3A4 inhibitor. But in some of your data, it looked like it increased the area under the curve of flibanserin of about 40 percent and did have some sedation-related effects that looked somewhat similar to some of the moderate CYP3A4 inhibitors.

So in the label, there is this distinction between a contraindication for moderate and severe CYP3A4 inhibitors but just a cautionary on hormonal contraceptive use. So I was wondering how the data matches up to the label and does that support what's on that draft label.

MS. TORRENTE: Thank you. We did very

carefully consider knowing that a large percent of our population would be taking hormonal contraceptives, so we put a good bit of thought, and the effects are different than in moderate CYP3A4s.

The first thing we looked at, of course, was whether flibanserin had a negative effect on the efficacy of the contraceptive, and it did not. So we did do a study on the PK flibanserin and how it affects the two components of hormonal contraception, and as you can see no effect.

That's consistent with the several pregnancies that we had in our studies. They are evenly distributed between placebo and flibanserin, so that was our first point of comfort.

We then did do a pharmacokinetic meta-analysis of phase 1 studies with and without hormonal contraception. I'll show you those data. So you're right that's it a 30 to 40 percent increase in Cmax and AUC, not unexpected with a mild CYP3A4 inhibitor. This is just for context, 10 studies, 261 subjects.

That does have the corresponding increase that you mentioned in sedation-related adverse events, still within a range that I think are tolerable if the patient is advised of the events. What we did do to assess this more carefully was look at the driving study. And there, we ensured inclusion of at least half the subjects on hormonal contraception to see if that sedation would result in next-day impairment.

The SLDP, which you remember is that weaving measure, no difference between with and without hormonal contraception. So we see the patients on hormonal contraceptives still driving better than placebo, so that again gave us great comfort.

What we've done in the package insert is to advise of no pharmacokinetic interaction on the CYP3A4s; so no pharmacokinetic interaction on the hormonal contraception. But then in drug interactions, to specifically call out oral contraceptives when saying that mild CYP3A4s could show a rise in dizziness, somnolence, or fatigue.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: I have a few questions all about safety. The first is, why was the alcohol study conducted almost exclusively in men since the product is being sought for approval in women?

The second is just I guess a little bit further to follow up on the last question, if we could see information about rates of ADEs stratified by concomitant medication use for products other than contraceptives; that is were rates of ADEs similarly higher for individuals taking other medicines or looking at all concomitant medicines rather than oral contraceptives alone?

Then the third is just about the assumptions that are being made about the sedation-related or other ADEs among the one-fourth of subjects that, if I understood correctly, dropped out of the study.

I think there's obviously some reason for concern that people that drop out are different from those that don't, and I'm just interested in what assumptions are made about the rates of ADEs

among those that aren't observed for the duration of the study.

MS. TORRENTE: Let me try to walk through those for you. In terms of the alcohol study, we didn't have the foresight to require only women, so the study also didn't require only men. As it happened in the enrollment, 22 men and 2 women enrolled.

I would like to take a moment to clarify the moderate drinker. Over half of the patients reported 5 drinks per week, which is considered a light drinker by alcohol study standards. So even though they were men, there were a large percentage of light drinkers.

The two women who enrolled, I can tell you that they had lower BMI, neither were on hormonal contraception, and their PK was not tremendously different from the men in the study. But, of course, there's only two of them, so there's very little to say.

The thing I will say is we would be concerned that the Alcohol Challenge Study was an

insufficient challenge if we had not seen events in the men. But because we did see events, I think it was a sufficient challenge likely because of the quantity of alcohol and the rapidity with which it was taken at 10 a.m. So we do think it's an adequate alcohol challenge that can inform our labeling even for a drug intended for women.

I think I'll move on to your next question, if that's satisfying to you. That's the best I can tell you on the alcohol in men.

The safety by concomitant medication use, other than hormonal contraception, we've looked at those categories of drugs that were most frequently taken in our studies, so triptans, SSRIs, aspirin and NSAIDs and antihistamines, these are the typical products that we would expect of this population, which is otherwise generally healthy, to be taking.

If I can show you the triptan data first, I think you're probably accustomed to this pattern of slides that we're showing you, placebo rate differences in the gray between users and nonusers

of triptans with placebo, and then in the green, the rate difference for flibanserin users versus nonusers of triptans.

You can see an uptick in some events, less in other events. Overall, we don't really see a pattern here, recognizing there's a small number of subjects, 61 versus 55, that we're talking about, but no real pattern.

The next one I'd like to show you is SSRI/SNRI, again small numbers here. What we do show, again, is overall, an actual decrease in the rate difference. We see this even in our SSRI/SNRI safety study, that the addition of flibanserin doesn't so much exacerbate the adverse effects, as somehow ameliorate them or at least cause no change. And that's I think seen here with the notable exception of anxiety.

For aspirin and NSAID use, we have substantially greater numbers as we would expect in this population; in the 500-range in both groups and some increase in some events.

The final one I'll show you is the

antihistamines, 300 patients per group on antihistamines, so again a number we think is consistent with the population and small increases in dizziness, somnolence as one would expect with two sedating drugs.

I think your third question was how were sedation-related adverse events dealt with in dropouts? Can you clarify for me if it's a statistical question?

DR. ALEXANDER: Well, just the assumptions that were made, what assumptions -- what should we think about the 25 percent of people that weren't followed through to study completion?

What assumptions were made about the rates of adverse events in them, and then do you have any reason to believe that the rates of adverse events would differ among the one-fourth of people that discontinued the study drug versus the three-fourths that did not?

MS. TORRENTE: The rates of adverse events, I think we do know that the sedation-related events do come on early. One way we've looked at this is

when patients have been on the drug for a while, are they having fewer of these events? It doesn't directly answer your discontinuation question, but we do see these events coming on early and then falling off over time.

In terms of how we handled the data for the patients who dropped out for adverse events or any other reason, we used an LOCF statistical model and then did a series of more rigorous and conservative sensitivity analyses for all missing data.

DR. LEWIS: Thank you. Dr. Hanno?

DR. HANNO: Thank you. I have three brief questions. One regards blinding and the issue of subtle unblinding due to side effects. Were participants asked whether they thought they were on drug or placebo after the trial?

Second, has there been any information on safety in the first trimester since I would think some of the women on this are going to get pregnant? And third is a question related to diagnosis and patient unrealistic expectations, which I see all of the time in men.

In this study, the average baseline SSE per month was almost 3 episodes a month. How many SSEs per month would indicate that a patient is not a candidate for this medical treatment?

MS. TORRENTE: Thank you. I'll try to handle those in the order that you've asked them. The first in terms of unblinding, whether patients were asked, they were not. We did not assess unblinding by patient query.

Information in the first trimester, I can give you information on pregnancies generally, but I don't believe that we have it broken out by trimester. I can see if we can get that for you over the break if that would be helpful.

Then your last question, which was patients having 3 SSEs, or actually 2.5 at baseline, and sort of how much SSE would be -- could you clarify what you asked?

DR. HANNO: Yes. In one study, I think there were 2.8 SSEs at baseline. I mean, a lot of men think they should be having sex every night, and if they're not, that's not normal. And a lot

of therapy is related on just realistic expectations.

So I'm just curious, looking at a lot of the information on this, I would've thought most of these women would not be actively engaging in sex at all hardly. Here, they're having 3 episodes a month. How many episodes of satisfying sexual events per month would make you say that this is not the correct diagnosis? Because diagnosis is going to be a major problem with the drug, I think.

MS. TORRENTE: If I can answer in three ways, unfortunately, not -- and I'll try to make it short. But first, the notion of whether SSEs or any number of them indicates that the condition exists or that the condition has been adequately treated, I think Dr. Kingsberg might just give us an insight on that. And then I'll ask Dr. Portman to address baseline SSEs and their adequacy generally.

DR. KINGSBERG: Actually, sexual activity is not in the diagnosis. In fact, women coming in with HSDD are having sexual events. Most of them

have been in long-term relationships and will choose to have sex for a variety of reasons. What we think of as SSEs are essentially downstream events of what sexual desire is.

As we think about, in fact, the idea of HSDD impairing the ability to have sexual events, we know that women can have a satisfying sexual event. And what I tried to show earlier is that what women are missing is the desire, the wanting, the appetite for sexual activity. And women will choose to have sexual events that eventually are satisfying for a variety of reasons. What they miss is the reward system that then wants them to want it again.

So I think that what we're looking at is the change in distress. And for realistic expectations, women come in already having sexual events; they're not expecting to have sex every day as sort of a sign of improvement. What they want is a restoration of what was normal for them, which is some wanting to want.

MS. TORRENTE: And then I wonder if

Dr. Portman can walk us through just the baseline SSEs, and then I'll conclude with your comment that the diagnosis is going to be an issue to just show you a screener we have to try to make that not an issue. Dr. Portman?

DR. PORTMAN: So I think it is a little bit confusing looking at SSEs as definitional for the diagnosis.

If I could put up the definition just to remind you, and as Dr. Kingsberg mentioned, that sexual activity per se, the amount of sexual activity, the number of events is not definitional. It can be a marker for activity. And in fact, that's really why in the FDA draft guidance, which is no longer online, in 2000, that they recommended the SSE because it was an objective counting.

We do believe that we need an objective counting measure as an objective measure of frequency because, as Dr. Kingsberg said, it is a downstream effect but not the defining characteristic of HSDD.

Here, you see that while there were some

women -- you mentioned the average of 2 to 3, and that's largely driven by the mean, but you see that close to half or over half were having 2 or less. And you have to remember that this population, these are 36-year-old women. And we could look at normative data from either the Kinsey Institute or other organizations, but certainly 2 events per month is clearly a sign of distress.

What's even more important is that even if a woman is reporting an SSE, a satisfying sexual event, we heard here at the patient-focused meeting last October that women often said, I was satisfied because I satisfied my obligation.

So it didn't have a whole lot to do necessarily with her own personal satisfaction, although these are not women who have necessarily orgasmic or arousal disorder. So once they engage in activity, it's pleasurable. That is not the part of the dysfunction. It's the total lack of interest and receptiveness and responsiveness to her partner's approach.

You remember that by definition, as part of

entry to the study, they really couldn't have that feeling of wanting. In fact, many of these patients, their partners stopped approaching altogether, and then they either didn't participate at all, or it was less than half the time, and almost always out of a sense of obligation.

So while the SSE is a helpful marker of frequency, and it's a nice objective ordinal counting measure to help us to see that we do see increased activity, but by definition, it is not necessary to be part of the condition.

So I think that that certainly helps put it into context. The fact that even though it is a downstream effect, it is susceptible to that placebo response that we saw in all studies. It still demonstrates statistical significance throughout the development program. It shows that even though it's a little bit of a blunt instrument, it still demonstrates that downstream, after you've improved desire and reduced these patients' distress, they are engaging in more activity.

Much of that is also dependent on partner initiation as well. So it's a little confounding, but it's helpful to see consistency throughout all trials.

DR. LEWIS: Thank you. We're running short of time and have to prioritize those who haven't asked questions yet. I'm going to ask Ms. Orza to ask her question.

DR. ORZA: Thank you. Dr. Orza. I actually have half a dozen questions, but I will ask only the first couple and hope that I can get back in the line.

The first one is just a quick technical question. Were all of the women in the study, were they all in relationships with men or were there some who were in relationships with women, and can you show us that breakdown?

The second one is, part of the reason that this is such a challenging instance is that when FDA approves the first drug for this condition, they will, in effect, be setting the standard for all the drugs that come after it.

So my question is for the clinicians in the company. Is the standard that would be set, if FDA were to approve this drug, a standard that you think would serve your patients well in terms of the efficacy and safety and the risk/benefit equation?

Then lastly, this is a very narrowly defined indication, and it was studied in a very well-defined and fairly narrow group of patients, and I'm wondering what your marketing data shows about the 10 percent of women that you're talking about who have this condition, where the demand will be coming from outside of the population in which we really have data on.

MS. TORRENTE: Thank you for those questions, and I'll try to answer them as quickly as I can. All of the subjects in the study were in stable monogamous heterosexual relationships. We did not enroll any homosexual women in our trials.

At the time that these studies were initiated, the key symptom endpoints were not validated as homosexual tools, so it wasn't able to

be done at that time.

In terms of setting the standard, I'll answer your third question, then ask Dr. Portman since you asked for a clinical perspective. What I will tell you is that the refusal to approve a drug will also set a standard by which people will not want to investigate further drugs if the standard is too high or unattainable. But I'll ask Dr. Portman for his clinical perspective.

In terms of the narrowly-defined population, we did take this committee's advice to heart that was given in 2010 and dramatically expanded the prohibited medications to make sure this was a generalizable population.

I think what you're asking more is, is there going to be a lot of off-label use in other areas, non-HSDD? That is a key part of our REMS strategy, is to ensure that this product is used for premenopausal women who have HSDD.

Not only is it part of the REMS, it's one of the reasons that we've chosen to mine that prescriber data that is out there, not just the

typical REMS assessment, so we can know are women in the ages of 60 to 70 getting the drug; are women with CYP3A4 inhibitors getting the drug? And we can look at all of those off-label cases.

So the best we can do is market it responsibly and then test to see how it's being used and adjust. So for the last part, I'll just ask Dr. Portman.

DR. PORTMAN: So this is a condition that's very well-characterized. It's in the sexual medicine literature. But you're right, as a new therapy comes to light for the first time, there will be some issues in diagnosis and appropriate prescribing. And I think we've seen that on the male side where typically you saw first utilization with doctors who are comfortable with their patients' urologist. And then once that's established and there's more educational opportunities, you see the broader community where there's clearly a need because not every -- we don't have enough urologists in the country to take care of all men with sexual dysfunctions, nor do we

have sexual medicine specialists to do that.

So we do certainly welcome the community doctors to see this and treat it because it is something that certainly in my discussions with doctors across the country, they see quite often. In fact, probably 7 percent of women can be diagnosed with this condition based on strict criteria.

Not everybody is going to use that strict criteria, but the sponsor has developed a screener -- and this is something that we are all familiar with other disease states -- that has been validated compared to expert interviewers, face-to-face structured interviewers who are very well aware of the condition. And there was very strong correlation, 85, 90 percent sensitivity and specificity.

So just quickly, the DSDS allows the clinician who -- this is something that they're familiar with. The patients are talking about it, but they're not quite sure whether or not she's appropriate. They simply ask four yes or no

questions:

In the past, was your level of sexual desire interest good and satisfying? Yes, meaning they don't have lifelong low desire. Has there been a decrease in that? So it's an acquired disorder. And are you bothered by it? Is it causing you distress? So therefore, treatment seeking, would you be interested in improvement and therefore be open to therapy?

So those are the critical four factors to diagnose generalized acquired HSDD. You don't have to be an expert in sexual medicine to do that. And then question 5, a multilevel discussion, really helps you clarify whether or not there's other mitigating factors.

I think that those of us who take care of patients either in OBGYN or primary care, we know our patients well; we know what's going on with their relationships. You can sense that there's a situational situation, or if there's a medication, or if there's another confounding medical condition. I think that this is going to be very

helpful for clinicians, and I don't think that there's any major hurdles for doctors to be able to make this diagnosis and treat appropriately and responsibly.

DR. LEWIS: Thank you. We are running out of time. We're going to take a couple more questioners, and then have a break and see if we can come back to more questions if there are more questions later. Ms. Aronson?

MS. ARONSON: Thank you. Slide 67, please. I do have a follow-up question about the pregnancies. It looks like just 114 had any dose of -- you mentioned the pregnancies. Can you tell me about the outcomes of those pregnancies --

MS. TORRENTE: Sure.

MS. ARONSON: -- thinking of safety. And I'm thinking potential infertility patients may be thinking of the use of this drug.

MS. TORRENTE: I see. So we did first look at nonclinical signals of reproductive health and toxicity and saw no concerning signals there. In our clinical studies, effective contraception was

required, so we wouldn't have expected to see very many pregnancies. Women wishing to become pregnant were excluded.

So really, I'm not going to have very much data to directly support women in an infertility space and what they would like -- whether the therapy would be used in them and how it would be used.

I'll tell you that we did have 67, I believe, pregnancies in the study evenly distributed percentage-wise between placebo and flibanserin. There were 2 congenital anomalies in the flibanserin group, fairly common congenital anomalies that are consistent with the rates in the general population.

Just because the chair, I'm sure, won't allow me, I could call a clinician to talk about infertility but -- yeah.

DR. LEWIS: Thank you. We are having time challenges. Dr. Leggio?

DR. LEGGIO: I have a question regarding phase 3, 147 study. Can you clarify the definition

of a drinker versus nondrinker and if you saw a difference between drinkers and nondrinkers in terms of dropouts?

Also, I have a brief follow-up question regarding the drug alcohol interaction study. It's unclear to me why it was not conducted a priori in women, and if you can comment on why it was so difficult to recruit women. Thank you.

MS. TORRENTE: Can I just clarify your question about the drinkers/nondrinkers in our 147 study? What was your interest? I know your one interest was the definition, but you had a second question about that?

DR. LEGGIO: Yes. The second was if they were different in terms of dropouts between the drinkers.

MS. TORRENTE: In terms of dropouts, I see. Gosh. I'm not sure we have the second. I can tell you that in terms of in 147, so in all the studies, women were just asked at baseline whether they consume alcohol. It was not a restriction for being in the study. And then in terms of

drinkers/nondrinkers, they were further categorized into how much alcohol do you drink a week, and it was, I think, 1 to 3 drinks, was everyone who said they were a drinker was in that 1 to 3 drink category, and no one self-reported as being higher.

During the study, of course, we didn't monitor were they drinking concomitantly with an adverse event or any of that. And I don't think we have a drinker/nondrinker by dropout. I can try to get that for you.

In terms of the alcohol study, we have a sense that women tend to be lighter drinkers. The study required 5 to 21 drinks per week at baseline. And maybe if we had recruited closer to a college campus or something, we would've been more successful in getting more women into that study. But unfortunately, there was an emesis concern with drinking so much alcohol in 10 minutes that we did exclude light drinkers. And I think looking back on it, maybe that's what caused people with 1 to 4 drinks, maybe mostly women, to not enroll.

DR. LEWIS: Dr. Perrone and then that will

be our last question.

DR. PERRONE: Thank you. For slide 14, I just had a question. The data that was presented pictorially in this was very impressive substantiating the disorder visually. My question is, Have you looked at the drug and enhancing the imaging in before and after pictures like this?

MS. TORRENTE: We do not have imaging studies on and off-drug.

DR. PERRONE: And my second question, from a safety standpoint, the data on alcohol is interesting and important. Increasingly, we're now facing other drugs with orthostatic hypotension such as marijuana. And I wonder what's going to happen to this, the sort of evaluation of future drugs in the setting of these kinds of interactions, all of the adverse events data that Dr. Alexander requested. I wonder if you could also address in the setting of marijuana.

MS. TORRENTE: What I'd like to tell you -- we thought very carefully about the alcohol data, both the data in our target population in

users/nonusers and then also that alcohol study. There is an interaction, and we thought hard about what is the best way to communicate that out. And in doing that, as we did with our REMS, we looked at what do other drugs do?

So first we considered should there be a contraindication, and we found those only in addictive drugs, opiates, Zyrem, the first drug out there for narcolepsy, contraindication. And then we found a tremendous mismatch of information among drug classes. So the PDE-5 inhibitors for erectile dysfunction, the chronic Cialis did the same study we did essentially and saw frank hypotension.

Their label says, "Do not use with substantial amounts of alcohol, more than five drinks at a time," and we considered this and wanted to be more conservative. This is still on the table for us as a way to go with the drug.

When we got into sleep aids, we see that the label in one place says don't use with alcohol, and then the other place, it tells you what to do if you do use alcohol.

Even in the antidepressants, the SSRIs and SNRIs, which maybe class-wise or closest to this drug, they say do not drink alcohol, but I don't think any of us believe that there's no depressed patient out there that ever has a drink.

So clearly, even that label language is intended to communicate a risk but not to entirely change and abrogate behavior. And so we struggled tremendously.

So where we came out with our label is to focus on what the risk is, and that is the risk of CNS depression and the risk of hypotension and syncope, and within the warnings for those risks to note that they are exacerbated by alcohol, separately in the label to say, you shouldn't use alcohol until you know how flibanserin affects you, mostly for the sedative effects.

Then separately, despite that the driving study was good, we said don't drive until the next day. Obviously, if one is drinking, they shouldn't be driving anyway.

So that's kind of where we came out. And

one of the reasons that we're happy to be in front of this committee today is we think there's tremendous confusion across the industry in how to label drugs for alcohol. And we're hoping that your deliberations today can help us come to a good place for package inserts, prescribers, and patients.

DR. LEWIS: Thank you. I'm sorry to those who haven't gotten their question in. We'll see if we can't have an opportunity later.

We'll now take a 10-minute break. Panel members, please be sure not to discuss anything about the meeting during the break amongst yourselves or with any member of the audience. We will resume at 9:57.

(Whereupon, at 9:47 a.m., a recess was taken.)

DR. LEWIS: I'll ask everyone to please take their seats so that we can get started. We did run over already, and we want to be able to allow everyone to have a chance to have their say and for discussions.

Could the committee members please take their seats, and everyone, please come to order so we can get started?

I'd like to ask folks to stop talking please, so we can start the FDA presentations. Thank you. We'll now proceed with the FDA presentations.

FDA Presentation - Ashley Slagle

DR. SLAGLE: Good morning. My name is Ashley Slagle, and I'm with the Office of New Drugs clinical outcome assessment staff. I'll share an overview of the efficacy endpoints and outcome assessments that were used in the flibanserin program, and then provide specific considerations from our evaluation of the key outcome assessments.

Co-primary endpoints in all three pivotal studies included a measure of satisfying sexual events, or SSEs, and desire. A daily electronic diary was used to count SSEs in all three studies. In study 71 and 75, the co-primary endpoint of desire was assessed using a daily electronic diary, and in study 147, the Female Sexual Function Index,

or FSFI, desire domain was used to evaluate the co-primary endpoint of desire.

The key secondary endpoint in all three studies was a measure of distress using a single item from the Female Sexual Distress Scale revised. Other assessments were used to evaluate exploratory endpoints, for example, the patient Global Impression of Improvement and patient benefit evaluation.

To assess SSEs, using an electronic diary intended to be completed every morning, women indicated if they had experienced a sexual event. If a sexual event occurred, the SSE primary endpoint was measure with the eDiary question, was the sex satisfying for you?

SSEs were standardized to a 28-day period using the formula shown on the slide. For example, if a woman entered 6 events over a 24-day period, the standardized SSE score would be 28 times 6 divided by 24 or 7 SSEs in that 28-day period.

To assess desire, the FSFI is a multidimensional, 19-item, self-report

questionnaire developed to assess female sexual function in women. The complete instrument consists of 6 domains, with the sexual desire domain based on items 1 and 2 of the questionnaire shown here and used as a co-primary endpoint in study 147, and again as a secondary endpoint in studies 71 and 75.

The instrument includes a 4-week recall period, meaning that patients are asked to reflect back over the past 4 weeks when responding to the questions in the instrument.

The desire assessment includes introductory instructions that direct respondents to define desire as being a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

Item 1 asks, how often did you feel sexual desire or interest, with response options ranging from 5, almost always or always; to 1, almost never or never.

Item 2 asks, how would you rate your level

or degree of sexual desire or interests, with response options ranging from 5, very high; to 1, very low or none at all. The 2 item scores are summed and raw scores are multiplied by a factor of 0.6 providing a sexual desire domain score that ranges from 1.2 to 6.

Study 71 and 75 used an electronic daily diary assessment of sexual desire as a co-primary endpoint. The daily electronic diary sexual desire question was, indicate your most intense level of sexual desire, and possible responses ranged from zero, no desire; to 3, strong desire with the resultant range for the monthly score calculated by adding the daily scores ranging from zero to 84 if data were entered on all 28 days.

Twenty-eight-day scores were standardized using a formula like that for SSEs that's shown here. Subjects were only allowed to enter data from the previous 24 hours.

The key secondary endpoint was the change in distress from baseline to endpoint as assessed by item 13 of the Female Sexual Distress Scale

revised, and specifically, item 13 asks, how often did you feel bothered by low sexual desire with response options ranging from zero, never; to 4, always.

Additional endpoints were included as secondary or exploratory endpoints to provide supportive information that can be informative to help interpret meaningful change.

The patient's Global Impression of Improvement is a single-item instrument asking patients to rate their condition today compared to when they started study medication, and response options range from 1, very much improved; to 7, very much worse.

Turning to our evaluation of the key assessments, FDA has consistently agreed to the assessment of SSEs using a daily eDiary and the assessment of distress using the FSDS-R item 13. And there are no remaining points of discussion related to these assessments other than questions about interpreting what constitutes meaningful score changes. We look forward to the committee's

input on this.

The remainder of this presentation will focus on some remaining questions related to the assessment and interpretation of sexual desire as assessed by the FSFI desire domain.

To support claims of treatment benefit, it's important that outcome assessments have adequate evidence of content validity. Content validity is supported by evidence from the target population, for example, patient interviews or focus groups, that the instrument adequately measures what is intended to measure in that clinical context.

This is important so that score changes on an assessment identified within a trial can be interpreted as clear evidence of the intended treatment benefit and so that the treatment benefit can be accurately described in product labeling in a way that's not potentially false or misleading.

The FSFI was initially developed using input from experts and patients with female sexual arousal disorder. Subsequent development work for the FSFI has been provided or conducted by the

applicant in women with HSDD, including two validation studies to address FDA's concerns related to content validity and recall period. The evidence suggests that patients generally agree that the instructions and items of the desire domain are relevant, important, and easy to understand.

Study participants were also queried about their preference for a recall period when assessing sexual desire. There was no clear preference for 1 to 2-week or 4-week recall, and a minority of patients favored a 24-hour recall.

One study indicated that 40 percent of women indicated they would answer differently if recalling the past 24 hours or 7 days compared to the past 4 weeks with example comments such as, because each week is different.

In the interest of time, I'm not going to go through the other measurement properties of the FSFI in detail but will summarize to say that most psychometric measurement properties of the FSFI desire domain appear adequate. However, there are

a few remaining questions related to content validity and recall used in the FSFI.

While important elements of desire are covered by the FSFI desire domain, items and instructions, concerns persist with the structure of the assessment that could impact interpretation of treatment benefit findings. Specifically, this domain includes what we call multi-barreled instructions making it unclear what element or elements may be driving the change identified on the assessment.

So for example, if only one component such as sexual fantasizing is actually increased in the women, but other components like wanting, initiating or feeling receptive to sex have not improved, a score change suggesting improvement could still be shown on this assessment. However, it is unclear whether change on a single component of desire represents a meaningful benefit to patients.

In addition, with a drug known to cause sedating effects like flibanserin, it's difficult

to determine the extent to which sedation itself contributes to receptivity to sexual advances and the observed changes in the FSFI desire domain score.

Patients in the qualitative research provide support that they are able to interpret and respond to the questions in the FSFI desire domain using the provided response options. However, it's not clear that women experiencing desire all of the time would identify this as a benefit or whether this could represent a different concern to women.

A 28-day recall period is used in the FSFI. The impact of this recall period on the ability to accurately reflect upon desire is unclear. For example, the longer recall period may increase noise in the assessment, thus attenuating treatment effects. With a longer recall period, it's also possible that patient recollection could be more heavily influenced by other feelings or experiences other than desire or by their more recent desire experiences.

In addition, it's unclear how to resolve the

discrepancy between the statistically significant improvement with the FSFI desire domain and the lack of statistically significant improvement with the daily measure of desire in studies 71 and 75.

Finally, as with the other assessments, it's not clear what constitutes meaningful improvement on the FSFI desire domain.

So you've seen that most of the remaining outcome assessment questions that we have focus on the FSFI sexual desire assessment, but we'd like to note that while we do not agree that the FSFI desire domain is an optimized assessment, it may provide interpretable findings of efficacy if there is a meaningful and reasonably sized magnitude of effect.

So we look forward to the committee's evaluation of the interpretation of efficacy based on the outcome assessments used in the flibanserin trials. Now, Dr. Sewell will discuss the efficacy findings.

FDA Presentation - Catherine Sewell

DR. SEWELL: Good morning. I'm

Catherine Sewell with the Division of Bone, Reproductive and Urologic Products. This morning, I will present to you FDA's analysis of the efficacy data, the responder analysis, and provide some conclusions.

For pivotal efficacy support, the applicant provided three randomized, double-blind, placebo-controlled, 24-week trials. As you've heard, there were two co-primary efficacy endpoints: change in number of satisfying sexual events, or SSEs, from baseline and change in sexual desire score measured by the eDiary in studies 71 and 75 and by the FSFI desire domain in study 147.

The key secondary endpoint was change in distress as measured by the FSDS-R question number 13. A responder analysis was also undertaken to inform the clinical meaningfulness of the treatment effect of flibanserin.

The key inclusion criteria are as follows. Subjects had to be at least 18 years of age, premenopausal, in a stable monogamous, heterosexual relationship for at least 1 year, and their partner

had to be present for at least 50 percent of each month.

Subjects had to have a primary diagnosis of HSDD of at least 24 weeks' duration, and they had to demonstrate sexual distress with a score of at least 15 out of a maximum 52 on the Female Sexual Distress Scale Revised and demonstrate low receptivity with a score of zero or 1 out of a maximum of 5 on the CDF.

Participants had to be willing to try to have sexual activity at least once monthly, be willing and able to use an eDiary and have demonstrated compliance with the eDiary, and be using a medically-acceptable method of contraception for at least 3 months.

There were numerous exclusion criteria. The key ones are here. There was a long list of prohibited medications, 5 pages long, in study 71 and 75 and 3 pages long in study 147.

Cytochrome P450 3A4 inducers taken currently or within 14 days of study drug administration was prohibited in all three studies. The same

prohibitions were for CYP3A4 inhibitors in studies 71 and 75, but these drugs were permitted in study 147. I would like to note that oral contraceptive pills, which are weak CYP3A4 inhibitors, were permitted in all 3 studies.

Patients whose sexual function was affected by any medication within 30 days were excluded from the study, and also women with certain health or medical conditions were excluded, for example, those with a history of drug dependence or abuse within the past year; those with issue with multiple severe reactions to psychotropic drugs; those who are currently or within the past 6 months pregnant or breastfeeding; those who had a recent major depressive disorder or any other psychiatric disorder that could impact their sexual function, compliance, or safety; those who had started non-drug psychotherapeutic treatment within 12 weeks of baseline; those who met other DSM-IV criteria for a primary diagnosis of another sexual dysfunction; or whose partners had an inadequately-treated sexual dysfunction.

There were also a couple of GYN exclusions. Women who were perimenopausal or postmenopausal were not eligible to participate, nor were women who had another condition that affected the female genital tract.

A total of 3,548 premenopausal women were enrolled in the three pivotal efficacy trials; 1,227 women received flibanserin, 100 milligrams PO qhs, and 1,238 received placebo. These two numbers obviously don't add up to 3,548, and those other women received other doses of flibanserin during the development program.

The overall completion rate for all doses of flibanserin was 70 percent. It was 69 percent specifically for the 100-milligram dose. There was a higher completion rate for placebo, 78 percent.

The mean age of study subjects was 36 years. The vast majority were Caucasian and 8 percent were Hispanic; 55 percent had at least a college education. The mean relationship duration, as you've heard, was about 10.8 years, and the mean duration of HSDD was 5 years. As we've discussed

before, 39 percent of women were using some form of hormonal contraception.

Next, I'll present the efficacy findings. Just for a foundation, for efficacy, the analysis population was the full analysis set, which includes all women who were randomized, who received at least one dose of study medication, and had at least one efficacy assessment.

Missing data were estimated by the last observation carried forward method. The statistical analyses employed were the Wilcoxon rank-sum test and the rank-transformed ANCOVA for SSEs, and ANCOVA was used for the desire and the distress endpoints.

I would like to note that for co-primary endpoints of SSEs and desire, the comparison between baseline and end of treatment had to achieve statistical significance on both endpoints. I'd also like to note that going forward, the data that I present excludes subjects from two sites in study 75, which were closed by the previous applicant due to study misconduct.

For the first co-primary endpoint of SSEs at baseline, women had 2 to 3 SSEs per month. To address Dr. Hanno's question, there was no upper limit to the number of SSEs for inclusion in the study. Ten percent of patients had more than 6 SSEs per month, 2.4 percent had at least 9 SSEs per month, and there were some outliers with subjects having 16, 23, and 34 SSEs per month at baseline.

We have put on the slide the mean change, which was the prespecified endpoint, but because the data are not normally distributed, the median is the preferred measure of central tendency. So I'd to focus your attention on the median change.

With flibanserin, there was a placebo-corrected median increase of 0.5 to 1 more SSE per month and this was statistically significant in all three studies.

When desire was measured by the eDiary sexual desire score in studies 71 and 75, baseline was 11.9 out of a possible range of zero to 84. With flibanserin, there was a placebo-corrected

mean increase in desire of 1.7 to 2.3, which was not statistically significant.

When desire was measured by the FSFI in all studies but as a co-primary endpoint in study 147, the baseline was 1.9 out of a range of 1.2 to 6.0. With flibanserin, there was a mean increase in desire of 0.3 to 0.4, which was statistically significant.

For distress, baseline was 3.3 on a scale of zero to 4, and with flibanserin, there was a mean decrease in distress of 0.3 to 0.4, and this was statistically significant in the three pivotal trials.

We conducted exploratory subgroup analyses, and through these analyses, there was no subgroup in terms of severity of baseline SSEs, desire, or distress that could be identified deriving a greater treatment effect in order to maximize the benefit/risk calculation. We also conducted a responder analysis, and we acknowledged that there is more than one way to evaluate clinical meaningfulness, but our responder analysis is one

of them.

For our responder analysis, we used the patient Global Impression of Improvement, which has been discussed before. Subjects answer the question, how is your condition today, meaning decreased sexual desire and being bothered by it, as compared to when you started study medication and are scored on a scale of 1 being very much improved to 7 being very much worse.

We performed a receiver-operated characteristic analysis using a logistic regression model plotting the PGI versus the change from baseline SSEs, desire, and distress in order to find an optimal cutoff point on the ROC curve.

We used 2 points on the PGI to determine this, the PGI of less than or equal to 3, which means a subject was at least minimally improved, versus a PGI of greater than or equal to 3, which means they had no change or were worse, and a PGI of less than or equal to 2, which means the subject was at least much improved, versus greater than 2, which meant they were only minimally improved, had

no change, or were worse.

The model was fit on all subjects, and the cutoff point was chosen at the site that maximized the sum of sensitivity and specificity. A subject was counted as a responder if they were at greater than or equal to the cutoff point and a non-responder otherwise.

The next two slides present tables for the percent responders. The first slide is the PGI of less than or equal to 3, which means that the subjects were at least minimally improved. So as we've discussed before, there is a robust placebo response on all the endpoints in all of the studies.

If we focus just on SSEs, the percent responders, or the treatment difference that can be attributed to flibanserin, is from 10 to 12 percent, for FSFI desire, it is from 10 to 15 percent, and for distress, from 9 to 13 percent.

When a PGI of less than or equal to 2 is used, which means that the subjects were at least much improved; again, there is a modest placebo

response in all of the studies, in all of the endpoints. For SSEs, the treatment difference or the percent responders that can be attributed to flibanserin is 8 to 9 percent, for the desire domain, it is from 10 to 13 percent, and for distress, 7 to 13 percent.

The onset of efficacy -- you've seen these graphs before -- is from 4 to 8 weeks. If you look at the graph in the top left corner for SSEs in study 147, you can see there's onset of efficacy by 4 weeks, some continued improvement by 8 weeks, and then it begins to plateau.

The pattern is the same for studies 71 and 75, the same for the desire endpoint, and of course, though the slope is different for distress because we're reducing the stress, the pattern is the same.

In summary, flibanserin 100 milligrams qhs has demonstrated efficacy across the three pivotal North American trials for the endpoints of SSEs, FSFI desire domain, but not the eDiary desire domain, and the FSDS-R question 13 distress score.

The benefits are numerically small though they're statistically significant. There is no definite subgroup, which might derive a greater treatment effect. Hence, FDA is seeking input on whether these observed effects outweigh the safety concerns that will be described in the upcoming presentations.

Next, Dr. LaiMing Lee is going to discuss the pharmacology.

FDA Presentation - LaiMing Lee

DR. LEE: Good morning. I'm LaiMing Lee, clinical pharmacology reviewer. I will discuss intrinsic and extrinsic factors that increase systemic exposure of flibanserin and its impact on safety.

The clinical pharmacology for this NDA is quite extensive and includes appropriately 25 phase 1 studies. For today, I will present major findings from clinical pharmacology studies that are applicable to the proposed patient population.

This presentation will include a description of flibanserin pharmacokinetics, characterization

of the exposure response and phase 1 safety; dose response and phase 3 safety factors such as drug-drug interactions and loss of CYP2C19 enzyme activity, which was not discussed by the sponsor nor included in the briefing package, that also increase flibanserin exposure; and major safety findings from phase 1 studies reviewed by the Office of Clinical Pharmacology.

The proposed product is an immediate release tablet following a single 100-milligram dose of flibanserin in 8 healthy premenopausal women. The mean maximum concentration Cmax was 419 nanogram per mL.

The mean total exposure characterized by AUC zero to infinity was 1543 nanogram hour per mL with a median time to reach the maximum concentration, Tmax, was 0.75 hour with a range from 0.75 to 4 hours, and the mean half-life was approximately 12 hours. Following once daily doses of flibanserin, the accumulation was 1.4. Flibanserin is metabolized mainly by CYP3A4, and to a lesser extent, CYP2C19.

The figure shows the dose proportionality for flibanserin pharmacokinetics. This was a single dose, ascending dose study in 6 to 8 premenopausal women using flibanserin tablets under fasting condition. The blue bars show the maximum concentration, Cmax, and the purple bars show the area under the concentration time curve, AUC zero to infinity.

For 100 to 250 milligram, we observed dose proportionality for Cmax meaning that as the dose increased, the maximum concentration increased proportionally. For AUC, the change in exposure appears to be greater than dose proportional.

In the phase 1 dose escalation study, the most common adverse events were somnolence, dizziness and nausea, which are similar to those AEs in the phase 3 studies. The figure shows the percentage of subjects on the Y-axis who experienced common adverse events and as a function of dose on the X-axis.

Unlike phase 3 studies, the majority of phase 1 studies are not powered to address safety.

This phase 1 study does show a dose safety response association. A greater percentage of subjects experienced adverse events as the dose and exposure increased.

Somnolence in purple was significantly higher with flibanserin 100-milligram compared to placebo. Dizziness in green and nausea in orange were more prevalent at 150 to 250 milligram. The doses proposed for this dose escalation study were at 100 to 300 milligram. Due to severe AEs in subjects taking 250 milligram flibanserin, the 300-milligram dose was not evaluated.

Blood samples to assess flibanserin concentration were not taken during the phase 3 studies, so we were unable to conduct an exposure of response analysis. This figure shows an association between dose and common safety issues from five phase 3 studies. As the dose was doubled from 50-milligram to 100-milligram, the percentage of patients experienced dizziness, somnolence, and nausea and fatigue increased almost twice. The proposed dose is 100-milligram to be taken at

bedtime.

The extrinsic factors that increased flibanserin concentration include drug-drug interactions with strong, moderate or weak 3A4 inhibitors. The intrinsic factor that will be discussed here is a loss of 2C19 activity in 2C19 poor-metabolizers abbreviated as PMs and how it resulted in increased flibanserin exposure. 2C19 PMs refer to subjects with no 2C19 enzyme activity. Extensive metabolizers, abbreviated Ems, refer to subjects with normal enzyme activity.

The figure in this slide summarizes the change in flibanserin exposure as characterized by Cmax due to 3A4 inhibitors. The exposure change was compared to flibanserin alone in the respective study.

Oral contraceptives are considered to be weak 3A4 inhibitors as previously mentioned, and a meta-analysis was conducted using phase 1 data in women who received oral contraceptives and various doses of flibanserin concomitantly. Based on a geometric ratio, that was adjusted and dose

normalized, the flibanserin Cmax increased 1.1 fold compared to flibanserin alone in those who received flibanserin and oral contraceptives.

Fluconazole resulted in a 2.2-fold increase in flibanserin Cmax. The half-life of flibanserin was prolonged by 13 hours. With a strong CYP3A4 inhibitor ketoconazole given over 5 days, the flibanserin inhibition led to 1.8-fold increase in flibanserin Cmax, and half-life was prolonged by 7 hours.

Submitted in the original NDA was a study assessing the interaction of flibanserin with itraconazole, a strong 3A4 inhibitor. This is not presented here because the itraconazole dose was not optimal to maximize the inhibition of 3A4.

The figure in this slide summarizes the change in flibanserin exposure as characterized by AUC zero to infinity due to 3A4 inhibitors. Again, the exposure change was compared to the flibanserin-alone group in the respective study. Flibanserin AUC increased 1.4 fold with oral contraceptives, 7 fold with fluconazole, and

4.6 fold with ketoconazole. An increase in flibanserin exposure due to moderate and strong 3A4 inhibitors were accompanied with increased incidences of fatigue, dizziness, nausea and/or syncope.

So you're probably wondering, why did the moderate 3A4 inhibitor, fluconazole, increase flibanserin exposure more than a strong 3A4 inhibitor, ketoconazole? This will be discussed in detail in the next slide. And the reason for that is that fluconazole is a multi-enzyme inhibitor. It is not solely a moderate 3A4 inhibitor; it is a moderate 3A4, moderate 2C9, and a strong 2C19 inhibitor. The data suggested that in addition to 3A4, 2C9 and/or 2C19 may be involved in the metabolism of flibanserin.

From a safety perspective, the study evaluating the DDI between flibanserin and fluconazole stopped early due to severe AEs. There were three cases of severe hypotension, one of which is categorized as syncope. All events occurred approximately 1 hour after flibanserin

100-milligram was given with fluconazole. The clinical details of these cases will be presented by Dr. Easley in the next presentation.

The applicant was asked to address the contribution of 2C9 and 2C19 on flibanserin clearance with a phase 1 study. To address the contribution of 2C9 and 2C19 to overall flibanserin clearance, the applicant evaluated the pharmacokinetics of flibanserin in healthy premenopausal women with either 2C9 poor-metabolizing status, PM, or 2C19 poor-metabolizing status as compared to healthy premenopausal women with both 2C19 and 2C9 extensive metabolizing status.

2C9 PMs are deficient in 2C9 enzyme activity. Similarly, 2C19 PMs are deficient in 2C19 activity. The data suggested that 2C9 was not involved in the clearance of flibanserin. However, comparing the flibanserin exposure in 2C19 PMs to 2C19 EMs, we saw an increase in flibanserin exposure. The comparison would be analogous to comparing EM with and without a strong 2C19

inhibitor, and this study is new to the third review cycle.

In general, the mean increase in exposure in the EMs was 1.5 fold in Cmax and 1.3 fold in AUC. So this suggested that flibanserin is partially metabolized by 2C19. In one subject, once 2C19 PM had a Cmax exposure that was on 1.8-fold higher, AUC 3.2-fold higher, she had no clinical symptoms of hypotension or syncope.

In another case, a 2C19 PM subject had a Cmax of 2.1-fold higher and an AUC of 1.2-fold higher; she did experience syncope, and this case will be shown with other cases of syncope in a following slide.

We have concluded that 2C19 is partially responsible for the metabolism of flibanserin. As a polymorphic enzyme, it is important to be aware of the frequencies of 2C19 PM status. Approximately 2 to 5 percent among Caucasians and Africans and 2 to 15 percent in Asians are 2C19 PMs. Some anti-depressants, anticonvulsants, and PPI inhibitors, proton pump

inhibitors, are 2C19 inhibitors.

As shown in the previous slide, an increased flibanserin exposure could occur in subjects with loss of 2C19 activity or those taking concomitant strong 2C19 inhibitors.

In the following two slides, I will briefly present cases of syncope in healthy subjects with no history of hypotension and not taking concomitant medications unless specified for a particular study.

The cases were captured from phase 1 studies reviewed by the Office of Clinical Pharmacology. Details on the cases of severe hypotension and syncope will be presented next by Dr. Easley.

This slide summarizes four cases of syncope in healthy premenopausal women who took flibanserin alone at the proposed therapeutic dose or lower. The first three cases of syncope occurred after the first dose of flibanserin. The first dose, the subject received 50-milligram flibanserin, lower than the proposed therapeutic dose. The PK data shows that it's actually lower than the exposure

you would see with 100-milligram even though it is slightly higher than the reference group.

In the second case, syncope occurred at the 100-milligram alone, and the third case, it occurred in an Asian female who had a loss of 2C19 activity. In the fourth case, syncope occurred on the third day after 3 daily doses of flibanserin. For the first and third cases where PK were available, the 2 women had higher exposure compared to the respective group as noted by the fold change of greater than 1.

This slide summarizes the cases of syncope in healthy premenopausal women who took flibanserin with an additional drug or alcohol. These were presented earlier by the applicant, but they are summarized here to be complete. Some syncope occurred following a single dose, 50-milligram flibanserin with a strong 3A4 inhibitor, a single-dose flibanserin 100-milligram with the multi-enzyme inhibitor, fluconazole, and a single-dose 100-milligram with alcohol.

Now, I will summarize our findings that are

relevant to the premenopausal population. Flibanserin is metabolized mainly by 3A4, and to a lesser extent by 2C19. Strong 3A4 inhibitor, ketoconazole, increased flibanserin exposure and Cmax, an increased it by 1.8 fold and AUC by 4.6 fold.

The multi-enzyme inhibitor, fluconazole, increased flibanserin Cmax 2.2 fold, AUC 7 fold. The mean flibanserin Cmax was 1.5-fold higher and AUC was 1.3-fold higher in subjects who are 2C19 PMs.

Generally, phase 1 studies are conducted in healthy subjects with no concomitant medications or comorbid medical conditions and with strict inclusion/exclusion criteria. In phase 1 studies, flibanserin was given in the morning, and subjects were monitored for AEs at the clinical site. In the phase 3 studies, flibanserin was dosed at bedtime. Dizziness, nausea, and somnolence increased with an increase in flibanserin exposure and dose.

There were 7 cases observed in phase 1

clinical pharmacology studies. There was one additional syncope case from a phase 1 dose abuse potential study.

The observed exposure increased and findings from DDI studies and other phase 1 studies suggested that co-administration of flibanserin with prescription and non-prescription 3A4 and 2C19 inhibitors, and/or other sedating drugs, will likely exacerbate dizziness, nausea, somnolence, fatigue, and/or syncope of flibanserin. Details of hypotensive and syncope events will be presented by Dr. Easley.

FDA Presentation - Olivia Easley

DR. EASLEY: Good morning. My name is Olivia Easley. I will be presenting FDA's findings of the review of the flibanserin premenopausal safety database.

The safety database in premenopausal women with HSDD consisted of a total of five, phase 3, randomized, double-blind, placebo-controlled trials. There was an additional phase 3 placebo-controlled trial conducted in women with

HSDD who were also taking SSRIs or SNRIs for depression.

There were 2 open-label 52-week safety extension studies, a 48-week phase 3 randomized withdrawal trial, 2 phase 2 randomized trials, select phase 1 studies, and there were a total of approximately 1500 premenopausal women with HSDD who were exposed to flibanserin 100 milligrams nightly in the phase 3 placebo-controlled clinical trials. The 100-milligram qhs dose is the proposed therapeutic dose.

So the major safety concerns that we identified following our review were the risk of CNS depression that occurs when flibanserin is taken alone or when it is used in the setting of concomitant administration of moderate or strong CYP3A4 inhibitors or with alcohol; the risk of hypotension and syncope with flibanserin alone and again exacerbated by moderate and strong CYP3A4 inhibitors and by alcohol; and finally, the risk of accidental injury.

Additional safety concerns we had with the

product were we noted there were increased adverse events when flibanserin was used in patients taking hormonal contraceptive products, which are also weak CYP3A4 inhibitors, also in patients taking SSRIs and SNRIs for depression, and triptan medications exacerbated the adverse event profile. Triptans are anti-migraine medications.

There was also an increased incidence of appendicitis observed in the phase 3 premenopausal database. There were 6 cases that occurred on women on flibanserin compared to none on placebo. This is a difference that we could not explain and could be due to chance. But again, as I said, we can't explain the reason for the discrepancy.

Finally, there was the uncertain clinical significance of dose-related mouse mammary gland carcinomas that were observed starting at 4 times the expected human exposure in a 2-year carcinogenicity study. Similar findings, however, were not observed in a 2-year rat carcinogenicity study.

This slide depicts the most common treatment

emergent adverse events that were observed in subjects in the phase 3 clinical trials in premenopausal women. The bars on the far right are the 100-milligram qhs dose. The most common events were dizziness, fatigue, nausea, CNS depression, which includes events of somnolence, sedation, or fatigue occurred in 21 percent of patients on the 100-milligram nightly dose.

The bars in the middle represent the 50-milligram bid dose, and you can see the tolerability did improve when the product was administered once nightly, which is the reason the applicant chose to pursue the once-nightly dose.

Premature discontinuation due to an adverse event occurred in nearly 13 percent of women on flibanserin, 100-milligram nightly, compared to about 6 percent on placebo. The most common adverse events leading to early discontinuation were dizziness, nausea, and somnolence.

One of our major concerns was hypotension and syncope associated with flibanserin. In phase 1 trials, all involving healthy women, at

doses of flibanserin less than or equal to 100 milligrams, there were 4 cases of syncope. One case occurred in a subject taking 50 milligrams, and the remainder in subjects receiving 100-milligram doses. I should note that in all cases, flibanserin was administered in the morning.

Vital signs were only recorded in one of the events. Case 3, the vital signs were normal, but the patient was in a supine position; heart rate is a little low, but the patient was unable to stand .

Two of the cases required intervention; in one case, fluid resuscitation, and the other patient was placed supine. The other two patients resolved without any treatment. And in all cases, patients did recover. All cases were considered to be drug-related.

In phase 3 trials in premenopausal women, the incidence of hypotension and syncope occurred in a dose proportional manner. The bars in the left -- this is the phase 3 placebo-controlled database. You can see placebo rate is 0.3 percent. This is the 50-milligram qhs dose, 0.4 percent, and

then a little bit higher in the 100-milligram qhs dose. The same trend is observed in the open-label, safety extension with a slightly lower incidence in the 50 nightly dose compared to the 100-milligram qhs dose.

In the placebo-controlled studies in premenopausal women, there were a total of 7 cases of outright syncope that occurred in woman taking 50 or 100 milligrams nightly. Six of those 7 cases occurred on the 100-milligram nightly dose. One of 7 cases resulted in concussion. The timing relative to initiation of treatment ranged from 11 days up to 93 days after starting drug.

We looked for risk factors. Two of the 7 patients did have a preexisting history of vasovagal syncope, but the remaining 5 cases had no medical conditions that would predispose to syncope.

Hormonal contraceptive products were used in 5 of the 7 patients, but otherwise, there were no medications that should increase the risk of syncope. And four of the 7 patients qualified

themselves as alcohol users at baseline, but the amount and timing of use relative to the events was not captured during the trials.

The next issue is flibanserin's interaction with alcohol. Because flibanserin does have CNS depression effects, and alcohol is a CNS depressant, the adverse event observed in phase 3 placebo-controlled trials in premenopausal women were stratified according to baseline drinking status.

Again, patients were queried when they enrolled in the trial, whether they used alcohol or not but alcohol use during the trial was not monitored nor was it prohibited.

You can see the bars on the far right, this is flibanserin-treated subjects who were drinkers. There's a higher rate of CNS depression, dizziness, hypotension, syncope, and insomnia. All of those are higher than in flibanserin nondrinkers or placebo drinkers and placebo nondrinkers.

To further explore the effects of alcohol on the safety and tolerability of flibanserin, the

sponsor conducted a dedicated drug interaction study enrolling 23 men and 2 women, all of whom were moderate drinkers. They were assigned to receive 5 treatments in random sequence, flibanserin 100 milligrams alone, low dose alcohol alone or with flibanserin.

Low dose alcohol is the equivalent of approximately 2 drinks in a 70-kilogram person, and then high dose alcohol, equivalent of approximately 4 drinks given alone or with flibanserin 100-milligram. Treatment was administered in the morning. Alcohol was consumed within 10 minutes. Vital signs and adverse events were monitored over the following 24 hours.

As you can see in this graph, the pink bars represent somnolence. There was a stepwise increase that was proportional to alcohol dose when alcohol was added to flibanserin, so 68 percent with flibanserin alone, going up to over 90 percent in the high dose alcohol plus flibanserin group. There's also an increase in hypotension observed when alcohol was added to flibanserin, though this

was not proportional to alcohol dose.

The last thing I wanted to point out is that the incidence of somnolence with flibanserin alone was greater than with either low-dose alcohol alone or high-dose alcohol alone.

There were 4 subjects in this trial who experienced clinically significant hypotension or syncope, meaning they required an intervention. All were men. All were in the low dose alcohol plus flibanserin group.

The treatment administered is shown in the column in the far right. You can see baseline blood pressures are here. They're all normal, and we have drops down to 72 over 44; this is standing. Another patient, a 22-year old man, 85 over 43, also in a standing position. This patient had 2 episodes of syncope, and one incidence is that blood pressure is normal. Then here in the second time, he has a drop down to 83 over 49 with an inappropriately low heart rate, and then a similar finding in this subject here.

Subjects were placed supine, in one case

Trendelenburg position. This patient required ammonia salts. They did gradually recover. The time of onset was between 1 and 4 hours following treatment.

Next issue is the interaction with CYP3A4 inhibitors. Because flibanserin is metabolized primarily by the CYP3A4 enzyme, the applicant conducted an interaction study with a strong CYP3A4 inhibitor, ketoconazole. They used the 50-milligram dose of flibanserin, which is less than the 100-milligram therapeutic dose.

Subjects received ketoconazole or flibanserin alone or the drugs together. This was conducted in women, and you can see that tolerability was worse in the ketoconazole plus flibanserin group. You have more nausea, vomiting, dizziness than when flibanserin was given alone. The rates, though, of CNS depression, and hypotension, and syncope are not exacerbated in the combination group.

The applicant also conducted a study with moderate CYP3A4 inhibitors, fluconazole, using the

therapeutic dose of 100 milligrams. This trial was conducted in women, and it had to be stopped early because of severe events of hypotension. That's why the sample sizes are lower in the combination groups.

Subjects received fluconazole alone, flibanserin 100-milligrams alone, or the two drugs together. As you can see, when the drugs were administered together, you have high rates of CNS depression, fatigue, nausea, and hypotension, and syncope compared to either drug alone. Again, in this trial as in the other phase 1 studies, the product was administered in the morning.

So as I mentioned, this interaction study had to be stopped early because of clinically significant hypotension. There was one case of syncope, a 41-year-old woman became unresponsive, blood pressure down to 64 over 41. She was transported to the emergency room for IV fluids. The remaining two cases were treated in the study clinic, but blood pressures over 80 over 49 in one and 73 over 41 in the other. All cases occurred

approximately 1 hour following dosing with flibanserin 100 milligrams and fluconazole.

Because many premenopausal women will be using hormonal contraceptive products and these drugs are known to be weak CYP3A4 inhibitors, the adverse events were stratified according to reported hormonal contraceptive product use. And you can see that in patients who are taking flibanserin 100 milligrams with a hormonal contraceptive, you do have exacerbation of the adverse events, of CNS depression, hypotension, syncope, fatigue, nausea, dizziness, all occurring at slightly to moderately greater incidences than in flibanserin alone, hormonal contraceptive alone, or placebo.

Finally, there was the issue of accidental injury. Because flibanserin did display higher incidence of CNS depression, accidental injury was a concern. When the phase 3 database searched for adverse events that could represent accidental injury, we see that in the placebo-controlled studies in premenopausal women with HSDD, there was

a very slightly greater incidence of accidental injury in the 100-milligram qhs group compared to placebo.

We also looked at the double blind portion of the randomized withdrawal trial, which was also involved premenopausal women with HSDD. The sample sizes are small, but you do see this same consistent trend of a higher incidence in injury.

So we wondered whether the CNS depression might be related to the accidental injury, was this contributing. So we looked among patients experiencing accidental injury, the proportion of those who reported sedations, CNS depression, hypotension, and syncope within 24 hours prior to experiencing injury. And you can see that that rate of concomitant events was higher in flibanserin; it's 24 percent in the 100-milligram group compared to approximately 9 percent in placebo.

Now, I will turn the podium over to Dr. Lehrfeld who will discuss the possible risk management options for the safety issues I have

presented.

FDA Presentation - Kimberly Lehrfeld

DR. LEHRFELD: Good morning. My name is Kim Lehrfeld, and I'm a team leader in the Division of Risk Management in the Office of Surveillance and Epidemiology at the FDA, and I'm going to present the risk management options for flibanserin.

My presentation will highlight the serious risks of flibanserin that could require risk mitigation beyond labeling, then provide an overview of risk evaluation mitigation strategies, or REMS, and present some risk management options.

As Dr. Easley presented, the most serious risk associated with flibanserin is hypotension and syncope, which can present with flibanserin alone or exacerbated when flibanserin is used with moderate or strong CYP3A4 inhibitors or when used with alcohol. I will address each of these situations in the following slides.

First, I'll discuss hypotension and syncope of flibanserin alone. Hypotension and syncope can

occur with flibanserin alone at therapeutic doses. However, at this point, patients at risk are not readily identifiable. Therefore, no specific advice can be offered on how to decrease the risk for an individual patient.

Due to the seriousness of the risk, additional risk management options beyond labeling for the healthcare professional and a medication guide for patients could be considered. However, any option will be limited to increasing awareness of the risk among healthcare professionals and patients but wouldn't prevent the occurrence of hypotension in the individual patient.

Next, I'm going to briefly discuss the serious risk of hypotension and syncope when flibanserin is used with moderate or strong CYP3A4 inhibitors. To review, dedicated drug-drug interaction studies showed increases in exposure by 4 to 7 fold when flibanserin was co-administered with CYP3A4 inhibitors. An increased exposure was associated with serious hypotension and syncope.

How can this risk be managed? First,

drug-drug interactions with flibanserin and CYP3A4 inhibitors will be addressed in product labeling. The applicant has proposed to contraindicate moderate to strong inhibitors, strong CYP3A4 inhibitors in labeling. In addition, a medication guide will be included to inform patients of the risks. The agency is also considering a boxed warning.

Additionally, because the moderate to strong CYP inhibitors will be contraindicated in the label, existing drug-drug interactions screening technology will be utilized to identify and prevent serious interactions. The healthcare system's existing drug interactions screening technology include screening by electronic medical records for prescribers, insurance company screening during prescription adjudication, and pharmacy screening prior to dispensing every prescription.

There are some potential limitations to drug-drug interaction screening. They include when patients use certain herbal products or nonprescription medications or when prescription

CYP3A4 inhibitors are written by a prescriber who did not write for flibanserin; both prescriptions are filled outside the insurance system and filled at different pharmacies.

However, drug-drug interaction screening technology is the accepted way to detect and address the many currently approved CYP3A4 contraindicated medications. Therefore, the agency believes this risk doesn't warrant additional risk management beyond labeling and drug-drug interaction screening technology at this time.

The last risk I'm going to discuss is the risk of hypotension and syncope when flibanserin is used with alcohol. As Dr. Easley presented, hypotension and syncope occurred in dedicated drug-drug interaction studies of flibanserin and alcohol, including cases which required medical intervention.

When considering whether additional risk mitigation is necessary, we considered that alcohol is a patient-dependent behavior. As shown in the table, the intended premenopausal patient

population does use alcohol.

In a 2013 SAMHSA survey, 56.9 percent of women between 18 and 25 are current drinkers and 50.1 percent of women 26 and older are. As concerning is that 31.4 percent of women between 18 and 25 and 14.7 percent of women 26 and older are binge drinkers, which is defined as having 5 or more drinks on the same occasion. This drug-drug interaction screening discussed previously will not detect this interaction. Therefore, additional risk management options could be considered.

To summarize my presentation up to this point, we are considering risk management options beyond labeling for hypotension and syncope with flibanserin alone and when flibanserin is used with alcohol. Since the risk management options for flibanserin include risk evaluation and mitigation strategies or REMS, I'd like to briefly review what a REMS is.

REMS are required risk management beyond product labeling. The FDA Amendments Act of 2007 gave the FDA the authority to require applicants

develop and comply with REMS programs if it is determined it is necessary to ensure that the benefits outweigh the risks. REMS can be required pre- or post-approval, and REMS are enforceable.

A REMS could include different components. First one would be a medication guide. Medication guide is FDA approved labeling for patients, and it's written in patient-friendly language and distributed with every prescription. They're used to inform patients about the serious risks of a product.

A REMS could also include a communication plan to inform healthcare professionals about a specific risk. They could also include elements to assure safe use, which I'll discuss on the next slide, and they must include a timetable for submission of assessments of the REMS.

There are six possible elements to assure safe use that can be part of a REMS. These includes certification or training for prescribers, certification of pharmacies, use of a drug in a limited setting such as an emergency room or a

hospital, dispensing of a drug with evidence of safe use conditions, required monitoring of a patient after administration of a drug, or the use of a patient registry.

It's important to note when thinking about a REMS with elements to assure safe use that the purpose is to provide safe access to drugs that would otherwise be unavailable and that the drug, which is shown to be effective but has a serious adverse event, can be approved only if the elements to assure safe use are required.

This slide shows the risk management options I'll present for your consideration. First, you could consider product labeling alone for flibanserin. This would include warnings and precautions about hypotension and syncope in the prescribing information for the healthcare professionals as well as a medication guide with patient-friendly language about hypotension and syncope for patients.

There are three REMS options the agency is considering, but there certainly could be others.

The REMS options I will present include a communication plan, a communication plan and pharmacy certification, and lastly, prescriber and pharmacy certification.

The first REMS option is a communication plan, which would include FDA approved materials used to inform healthcare providers about the serious risks or to aid in the implementation of a REMS. These materials are not directed at the patients.

Communication plans can include Dear Healthcare Professional Letters for likely prescribers. For flibanserin, this will be a large number of healthcare professionals with varied training, including primary care physicians, gynecologists, psychiatrists, and others. The dissemination of information could go to healthcare professionals through professional societies, and there's also the option to include additional materials, possibly including a safe use check list or a patient counseling tool.

One benefit of a communication plan is that

it does provide targeted risk messaging for healthcare providers about the serious risks. In addition, the prescribing information could be distributed with these materials.

There are also limitations to a communication plan. It will not ensure that every flibanserin prescriber who receives the information or ensure that those who receive it read it. In addition, it does not ensure that patients will avoid alcohol.

The second REMS option is a communication plan with the addition of pharmacy certification. Pharmacies will be required to train all dispensing pharmacists on the need to provide counseling to patients each time flibanserin is dispensed and to distribute the REMS educational-related materials to the patients.

The benefits of adding pharmacy certification are that it provides additional insurance that pharmacists are informed of the risks and that patients will be counselled specifically about the risk of hypotension and

syncope and the need to avoid alcohol while taking flibanserin. Limitations are that patient access may be decreased if patients are challenged to find a certified pharmacy, and this option also does not ensure that patients will avoid alcohol use.

The last REMS option is prescriber certification with pharmacy certification. Adding prescriber certification will require the prescribers acknowledge reviewing the REMS materials and agree to counsel the patient about the serious risks. In addition, it will ensure that prescribers are informed of the importance of proper patient selection.

This could be accomplished by including a safe use checklist as a tool within the REMS that emphasizes appropriate patients, including premenopausal women with the diagnosis of HSDD, no history of alcohol abuse, and the ability to refrain from alcohol use while taking flibanserin.

The benefits of prescriber certification are that it does provide additional insurance that prescribers have reviewed the risk information and

are aware of the need to counsel their patients about the risks. In addition, if the prescribers are encouraged to utilize a safe use checklist, they may be more informed about patients who are not appropriate candidates for flibanserin. Inappropriate patients may be identified and not prescribed flibanserin, thereby minimizing drug exposure to an individual patient and at a population level.

The limitations of prescriber certification are that screening patients for alcohol use or abuse may not be effective since patients historically fail to self-report or underreport alcohol use. Also, patient access may be decreased if patients seeking treatment are challenged to find a certified prescriber. And finally, additional counseling will not ensure the patients avoid alcohol use with flibanserin.

Now, I'm just going to briefly discuss the applicant's proposed risk management plan. They already discussed it earlier this morning and presented it, so this slide just contains a summary

of their plan.

They have a proposed product labeling, which doesn't include a boxed warning for hypotension and syncope, a communication plan REMS, and additional voluntary activities.

The agency's concerns with their proposal, first, are that the decreased sexual desire screener tool is a diagnostic tool, and it doesn't address the risk the REMS is intended to mitigate and is therefore not an appropriate material to include under the REMS.

Additionally, the applicant's proposed responsible launch and prescriber training materials are voluntary, which means the training materials will be not be reviewed by the agency, and these activities can be discontinued at any time without agency input or approval.

Finally, the communication plan REMS has limitations of all communication plans in that it is passive communication of the risk messages to healthcare professionals.

I presented three REMS options which add

different levels of assurance regarding awareness of the risks. But there are limitations of any REMS for hypotension and syncope with flibanserin alone since no risk factors or predictors have been identified and it is unpredictable when this event could occur during treatment.

Therefore, education of healthcare providers or patients through a REMS will not mitigate the occurrence in an individual patient. There are also limitations to any REMS to address hypotension and syncope when flibanserin is used with alcohol.

Mitigation of this risk is dependent upon patient behavior, specifically avoidance of alcohol by patients when approximately 50 percent of the intended patients currently use alcohol. Also, informing patients not to drink alcohol may not translate into patient understanding or safe patient behavior.

In conclusion, the serious risks which require consideration for a REMS are hypotension and syncope with flibanserin alone and flibanserin with alcohol. Each risk management option provides

different levels of assurance regarding the awareness of the risk.

The committee will be asked to consider whether a REMS is necessary and would it be able to ensure that the benefits outweigh the risks of hypotension and syncope with flibanserin alone and with concomitant alcohol use?

Next, Dr. Chang will provide summary comments for the agency.

FDA Presentation - Christina Chang

DR. CHANG: Good morning. My name is Christina Chang. I am a clinical team leader from the Division of Bone, Reproductive and Urologic Products. I would like to end the FDA's presentation this morning to the committee with a higher level summary of the data, and I'll try to distil for the committee some of the salient issues regarding this application.

To reiterate, the most important attributes of flibanserin will be the PK/PD attributes. For PK, after oral administration, the maximum plasma concentration is achieved very quickly, within an

hour. It has a long half-life of almost 12 hours, and the pharmacodynamic effects are primarily related to sedation.

Moving on to summary, this table summarizes the results from all three pivotal trials. Treatment with flibanserin was found to consistently and positively impact SSEs, and depending on the analysis, SSEs are increased from 0.5 to 0.8 -- 0.5 or 0.8 to 1 event per month.

For sexual desire, the findings were a bit mixed. When desire was measured by the FSFI desire domain using the 28-day recall, there was an improvement in the score of slightly less than half a point on the scale of 1.2 to 6. Although in the first 2 trials when sexual desire was measured daily, flibanserin did not beat placebo. With respect to distress, treatment with flibanserin consistently lowered the distress score also by about slightly less than half a point on a scale of zero to 4.

As you've heard from Dr. Easley, FDA's review of the phase 3 data identified three primary

areas of safety concerns, first, the CNS depression; second is clinically significant hypotension and syncope. Both of these safety signals can occur with flibanserin alone but are also amplified in the setting of co-administration with alcohol and many of the CYP3A4 inhibitors; thirdly, accidental injury which is possibly related to the first two safety issues.

Of these three safety concerns that were highlighted in the previous slide, I'll focus on the cases of syncope and clinically significant hypotension, and I'll start with phase 1 data.

A total of 8 syncope cases were noted in phase 1 studies. Additional details on each of these cases can be found in table 32 in your clinical memo in the FDA's backgrounder. Occurrence of all these events all correlated to the time point at which flibanserin concentrations peaked and all were considered causally related to flibanserin. Syncope occurred with flibanserin alone at doses ranging from 50 milligrams to 200 milligrams. Syncope also occurred with concomitant

administration of fluconazole, ketoconazole, and alcohol.

Four of these subjects required medical intervention such as intravenous fluid resuscitation and being placed in Trendelenburg position with their legs elevated. Despite all these therapies, one subject still required transportation to the emergency room.

In the phase 3 program, possibly related to the bedtime dosing, not as many cases were observed. In all, 7 syncope cases were identified, both at therapeutic dose, the 100-milligram dose, and the sub-therapeutic dose, 50 milligrams were involved. All of the cases involving 100-milligram flibanserin, the proposed clinical dose, are captured in table 31 of the clinical memo in the FDA backgrounder.

We note that the occurrence of syncope ranged from days 11 to days 93 from starting flibanserin, so tolerance to syncope does not appear to develop with continued therapy.

You'll recall from Dr. Sewell's presentation

that onset of efficacy may not be established completely until 48 weeks into starting therapy. Significantly, one subject suffered a concussion when she fell, and this injury qualified as a serious event.

Potential contributing factors for syncope were seen in some of the subjects but not all. For example, 2 had histories of vasovagal syncope; 5 took hormonal contraceptives; and 4 reported alcohol use at baseline. However, we should note that alcohol use was only captured at baseline and not prospectively or continuously assessed, so it's unclear whether these syncopal episodes were indeed related to the alcohol use.

Next, you'll see the five cases of clinically significant hypotension. All occurred in phase 1 and all required medical intervention. For cases in the alcohol study, please refer to page 72 of 159 pages overall in the backgrounder. For cases in the fluconazole DDI studies, please refer to page 55 of the clinical memo. So all together, we have 13 cases of syncope and

symptomatic hypotension from phase 1 studies and 7 from phase 3 studies.

Now, I'll turn to the benefit/risk considerations, and I'll offer the committee FDA's perspective as you weigh the strength and limitations of the available data.

First and foremost, the therapeutic context, we know that HSDD is a disorder than can seriously affect the quality of life in the woman and her partner. FDA has recognized that in the area of sexual dysfunction, there is an unmet need because there are no FDA approved medical therapies to treat decreased sexual desire in women or men.

One challenge we have seen in developing products intended to treat HSDD is that by definition, the condition is one of exclusion; a last choice, if you will, in the diagnostic algorithm.

Correspondingly, here, we have a clinical program that excluded women with other comorbidities and taking many other concomitant medications. Because of these exclusions, we are

asking the committee to opine on the generalizability of data from existing clinical database.

Next on the benefit as shown, if approved, flibanserin will be the first drug product to treat HSDD. Despite the shortcomings in studies 71 and 75 where a prespecified co-primary endpoint failed, flibanserin has consistently demonstrated treatment effects in SSEs and distress. The results of sexual desire scores based on the FSFI desire domain were also consistent. However, the treatment effects are numerically small, so we will be asking the committee for input on the clinical meaningfulness of the effect conferred by flibanserin.

Moving on to major risks, as I mentioned, there were 20 cases of syncope and symptomatic hypotension in all from the clinical program. Underlying causes for these events varied involving flibanserin alone, with the different doses and different drug or substance interactions.

Regarding injuries, we also found that the

incidence of accidental injuries that occurred in close temporal relationship with AEs of CNS depression and sedation was 2 and a half times greater in flibanserin-treated subjects than in placebo subjects.

As Dr. Easley discussed, there are other safety concerns. First, to a lesser extent than what was seen with alcohol or moderate/strong CYP3A4 inhibitors, many frequently used medications in the proposed target populations such as hormonal contraceptives, antidepressants, or triptans also exacerbated the adverse event profile. And as you recall, the list of prohibited medications in the phase 3 program amounted to 3 pages or 5 pages long, the implications I'm asking you to keep in mind.

Second, in the phase 3 program, there was an imbalance of appendicitis, not favoring flibanserin. Factors contributing to this imbalance are not known. And third, in the nonclinical program, there was a dose-related carcinogenicity signal of mammary carcinoma seen in

one of the two animal species. Additional nonclinical studies are not likely to further elucidate the clinical risk of breast cancer in humans. Again, the implications for women who have a personal history or family history of breast cancer is unknown.

Finally, I'd like to remind you of the dose escalation study from Dr. Lee's presentation, which show that flibanserin in doses greater than 250 milligrams will be poorly tolerated. This product has a narrow safety point margin.

Finally, I want to circle back and call your attention to the most serious risks identified in the program, namely syncope and clinically significant hypotension. The intended chronic use of flibanserin raises a number of concerns. Recall that syncope and hypotension can occur with flibanserin alone, at sub-therapeutic and therapeutic doses, and the timing of these events could not be easily predicted. Furthermore, these risks were amplified by concomitant drugs and alcohol use.

Complete avoidance of any of these of concomitant medications and alcohol may not be feasible. And as Dr. Lehrfeld alluded to, it's possible that none of these risk mitigation options could be sufficient to mitigate these risks.

We are seeking the committee's input on whether a REMS could adequately mitigate these risks to ensure that there is a favorable benefit/risk profile, and this concludes the FDA's presentation. The team from FDA will be happy to answer any questions from the committee.

Clarifying Questions to FDA

DR. LEWIS: Thank you. We'll now take questions for the FDA. If possible, please try to address your questions to a specific presenter and even slide number. So we will start with Ms. Aronson.

MS. ARONSON: Thank you. In the FDA briefing packet, page 10 2.2, there's a sentence that says that extent of exposure is increased up to 56 percent after a high fat, high caloric meal.

That hasn't been mentioned at all today and

I just wondered for that midnight piece of cheesecake or something -- I'm just wondering about the impact and -- with the half-life and all. I have a second question, too.

DR. LEE: Right. We did not include the information on the food effect, but the information is available in the briefing package. There was a food effect study that was conducted and submitted in the original NDA. The study was stratified by meal types and caloric content. Healthy subjects were taking light fat, low caloric-content food, moderate fat, moderate caloric-food, and high fat high caloric food.

The range in exposure change was about 17 percent to about 50 percent. We didn't see any AE differences, but again, phase 1 studies are not designed to capture safety data. So we did look at that, and in each group there are probably about 8 subjects. That review was six years ago with that study, so my memory might be a little bit old.

However, we did see that there was a change, and because this was dosed at night, and there was

no restrictions on food in the phase 3 studies, we couldn't extrapolate the impact of that on safety. But there was a range from 17 to about 50 percent, baseline fat and caloric content.

MS. ARONSON: Thank you. The second question I have -- and this is sort of a what-if perspective -- I'm just wondering about sort of the definition of sleepiness. One thing I worry about is because of the indication of this drug, could it be thought of as like a date rape drug? That's my worry, is about the sleepiness or the hypotension.

DR. NGUYEN: I think that's an excellent point, and that is something certainly at FDA we have thought about. I think it's an important piece of information that we will ask the AC panel to take into account.

DR. LEWIS: Dr. Perrone? And please state your name for the record?

DR. PERRONE: Dr. Jeanmarie Perrone. As I mentioned, I worked clinically in the emergency room department, and I see 7 or 8 cases of syncope per day. Most likely and most commonly, what we

see is young healthy women who have a fainting, brief fainting episode. If you look at their body weight, they tend to be normal to undersize.

On slide 8 of Dr. Easley's presentation, she did, I think, have BMI data on that slide. Two of the 4 people who had syncope seemed to have BMIs of 19, which is about on the high end of -- on the very low end of normal, almost underweight. Then, I think the sponsor had presented data in one of the slides of the overall group of people who were enrolled in these trials seemed to be a larger group of people with a more elevated BMI.

So I wonder if part of our risk mitigation needs to be target towards people who are on the low normal side of weight who would be at increased risk for syncope.

DR. EASLEY: Yes. That's a very good point. Again, in those thin women, they're already maybe at risk for syncope. But we haven't stratified the phase 3 safety database looking at whether there was a disproportion of women experiencing syncope who were thin, but it's definitely something to

think about overall.

DR. LEWIS: Dr. Whitaker? I'm sorry.

DR. LEE: Nor was there a dedicated phase 1 study to look at weight. That could be an option to consider, but we don't have that information.

DR. LEWIS: Dr. Whitaker?

DR. WHITAKER: Hi. Dr. Whitaker from the University of Chicago. I have a question specifically for Dr. Lehrfeld just to clarify the REMS and REMS with ETASU, make sure I'm thinking of it correctly.

I think a lowest level would be labeling, and then would be a REMS plan, and then would be REMS with ETASU. My question is just first a clarification question. Would the provider and pharmacy certification fall under the ETASU? So the more conservative measurement.

Then, just in the interest of consistency across medications, can you give us some examples of what other types of medications have the more stringent ETASU requirements, specifically drugs similar to this class that were discussed earlier

in the sponsor's presentations?

DR. LEHRFELD: So I will take the first question. Yes, the prescriber certification and the pharmacy certification are ETASU, so there would be restricted distribution. Determining whether our product needs a communication plan versus an element to assure safe use or no REMS at all, it's a complicated risk/benefit analysis individualized for each product, for each group of patients that it's going to be indicated, for each group of prescribers who are likely prescribers, dependent upon which condition and the severity of the condition you're treating, as well as the adverse event and the severity of the adverse event.

So I don't want -- I can't really answer the question about, you know, do we require ETASU for -- is it more conservative? It really is dependent upon how we want to get the risk messaging out.

It doesn't have to be dependent on how serious the adverse event is. It's hard to say

conservative versus not conservative. I would want to say it's a very individualized decision for each individual product.

DR. LEWIS: Thank you. I have a question. Vivian Lewis, University of Rochester. I have a question for Dr. Sewell. It's about efficacy. Was the efficacy stratified at all by baseline number of SSEs? I'm noting there was quite a surprisingly wide range.

DR. SEWELL: Yes. We did do subgroup analyses looking at the efficacy in terms of -- excuse me -- looking at the outcomes for efficacy in terms of SSEs, improvements in desire and reduction in distress by baseline SSEs, and there was no clear pattern of effect.

For example, if subjects had zero to 1 SSEs per month, they did not necessarily derive a greater benefit from flibanserin than subjects who had 1 to 2 SSEs per month or 2 to 4 SSEs per month.

DR. LEWIS: Dr. Orza?

DR. ORZA: Michele Orza. I, again, have half a dozen questions but will ask only the first

couple and ask to get back on line.

I think I'm remembering correctly that women would be taking fluconazole and ketoconazole for fungal infections. And it made me also think about medications for UTIs, and I wondered if any of those classes of drugs were studied since they might be widely used in the population taking this drug. That's the first one.

The second one is in the background materials, you mentioned that data from two sites were pulled out of your analysis because they were irregularities. I wondering if you could say a little bit more about that.

Finally, the breast cancer risk is kind of a showstopper for me. It wasn't mentioned at all by the sponsor, and it was mentioned almost in an off-hand way by the FDA people. So I'm wondering if you could say a little bit more about what we should make of the data on the breast cancer risk in the animal studies.

DR. CHANG: This is Christie Chang. I'll take the first question first regarding the other

concomitant medications.

We did recall that there were -- in the phase 3 program, there were women who used ciprofloxacin for their urinary tract infections. But we don't have any specific numbers or percentages to -- the numbers were too small to correlate to adverse events. But we can get back to you if you we have more information in the afternoon.

DR. EASLEY: Yes. I wanted to clarify. We did search the database for concomitant use of other strong or moderate CYP3A4 inhibitors, and there were very few patients who used anything that would be administered orally. Among those patients who did, the few patients who did, we didn't see any syncope or any other adverse events of concern that would suggest a correlation. But again, the sample sizes were so small, it's hard to know.

Sorry. What was your second question? The breast cancer issue was the third. What was your --

DR. ORZA: The study sites that you

disqualified their data.

DR. SEWELL: I'm sorry. What was your question about those study sites?

DR. ORZA: Just if you could say a little bit more about what was the nature of their disqualification.

DR. SEWELL: Sure. Those sites were actually closed by the previous applicant, not by the FDA, although the FDA did inspect those sites. And they were closed because of study misconduct in another trial, in study 84, which was not part of the trials that we used for efficacy.

There were things such as falsification of data, protocol violations, things of serious concern that Boehringer Ingleheim determined their data shouldn't be used, and we agreed with that assessment.

DR. CHANG: I'd like to come back to CYP3A4 inhibitors. We actually have backup slides from Dr. Lee's presentation. We have the most updated list of all available CYP3A4 inhibitors, including mild, moderate, and strong. I just wanted to show

the committee Dr. Lee's clinical pharmacology.

DR. LEE: Can you please show slide number 2? We are concerned about the interaction with strong 3A4 inhibitors. We have this list that was searched last year, and we find that there was about 25 strong CYP3A4 inhibitors.

If you go to the next slide, slide 3, we have moderate CYP3A4 inhibitors that are about equal in numbers. These are approved prescription drugs. We are not even addressing nonprescription drugs and other drugs that can have sedating effects.

DR. NGUYEN: Hi. It's Christine Nguyen. I want to address your question about breast cancer. The data, what we have there in animal, one of two studies. And the reason why that signal was important to us was, one, certainly, in this population, breast cancer, which is such a common malignancy in women, even those in reproductive age, is of important concern. And the second thing is we saw this outcome in exposures that was only 4-fold higher than the therapeutic exposure. So

that was something that made us pause and want to bring it up to the AC for consideration.

DR. CHANG: And I'll just add that the longest exposure in the clinical program is up to -- is a year to 18 months, and that, in our opinion, is not enough to assess the risk for breast cancer development.

DR. LEWIS: Thank you. Dr. Sturmer?

DR. STURMER: Thank you. Following up on the heterogeneity question that I think also follows up on Dr. Hanno's question earlier this morning, you said you didn't find any subgroup with a greater treatment effect. Did you find subgroups with smaller treatment effects? More specifically, in those with zero SSE, was the treatment effect the same as overall?

DR. SEWELL: There really wasn't a clear pattern of effect, so looking at SSEs at baseline and then looking at SSEs desire and distress outcomes -- I wonder if we could pull up those backup slides? It might be easier to show you.

Do you have the backup slides for efficacy,

and then if you could pull up the subgroup analyses?

MS. BHATT: What slide number?

DR. SEWELL: Starting with number 8. This one is looking at the outcome of SSEs, placebo-corrected, by baseline SSEs. All three studies are on the slide here. It's a little bit hard to read, but the first study, 71, next is 75, and next is 147.

You can see that we separated out the SSEs, not exactly into quartiles. As we said, the data is not normally distributed. Looking at study 71, if you see that for subjects who had less than or equal to 1 SSE per month, and then the next group is more than 1 to 2 SSEs per month, then more than 2 to 4 SSEs per month, and more than 4, you'll see that there are 2 Ns next to each subgroup. The first N is the number of subjects who are on the flibanserin, and the second N is the number of subjects who are on placebo. You can see that the Ns are quite small in some of those groups.

If we look at people who had less than or

equal to 1 SSE per month, say, in study 71, you can see that while the effect favors flibanserin, it appears less than, say, the group that had 1 to 2 SSEs per month. It's not a clear trend showing an improvement according to the number of SSEs. You can see that it's the same for studies 75 and 147.

We did do subgroup analyses for the outcomes of SSEs desire and distress by all of the baseline measures, and it's essentially the same. Do you want to see more of those analyses?

DR. STURMER: No. Thank you very much. That's very helpful. We can obviously discuss the absence or presence of trends here for a long time. I think that's exactly what I wanted to see.

DR. SEWELL: Okay. Thank you.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: I wanted to ask more about syncope. Given if the drug is approved, there's going to be hundreds of women who will have syncope from this drug, so I guess 3 quick questions.

One is, there seem to be a mix between orthostatic syncope and non-orthostatic. Is there

some understanding? Are these all orthostatic events, or are they happening when a woman is sitting in a chair?

The second question is the mechanism of the syncope, if there's some discussion of that. And third, there seem to be not only hypotension but bradycardia. I know that these are young women or young healthy, in some case, men, but I was quite surprised actually.

DR. EASLEY: So we don't actually know if all cases were orthostatic. We do have -- one patient, for example, was in a semi-recombinant position already, and she became unresponsive. They did not obtain her vital signs upon standing, so we don't know what the mechanism was.

We did also note the bradycardia and don't know if that's contributing to the syncope patients; heart rates aren't appropriately increasing. We don't know if it's a cardiovascular etiology or neurogenic cause. We don't know. It could be multifactorial.

DR. LEWIS: Thank you. Dr. Brandon?

DR. BRANDON: Thank you. My questions, I believe, are for Dr. Slagle. But I do want to comment on what I heard comparing this drug to a date rape drug.

I'm a clinician, I'm a psychologist, and a sex therapist, and I have worked with multiple women who've received date rape drugs and been raped. And I feel like it's disrespectful to compare these two.

What these women tell me is they can't move their body, they're confused, they've lost their memory.

(Applause.)

I'm hearing nothing on that level today about the side effects, so I just did want to comment about that.

I have a question. There was an implication that the sedation that flibanserin causes contributes to sexual receptivity. I find that to be confusing. Does that not mean that other medications with CNS depressant effects would also contribute to women's sexual receptivity?

Also, she's taking this drug right before she goes to sleep, and the effects I'm understanding occur about an hour into her sleep. So wouldn't that mean she'd have to wake up, have sex, go back to sleep?

DR. SLAGLE: Thank you. Thank you for the question. The intent of that was to suggest that we have concerns with the long recall period and that there could be other elements that are drug-related or patient population-related that could impact recall period. And sedation could potentially impact receptivity or it could also limit the ability of women to recall exactly what's happened over the last 30 days.

I'm sorry. The second part of your question?

DR. BRANDON: I haven't asked it yet. It was regarding the content validity concerns of the FSFI. My understanding is that one of the major concerns is that it could be measuring sexual fantasy as opposed to measuring desire. And I do have a question about that, because sexual fantasy

is a component of the HSDD diagnosis.

As a clinician, I help women cultivate sexual fantasy to use to trigger her desire or use during a sexual episode to increase her excitement. I was just concerned about why that is a problem?

DR. SLAGLE: That was an example. The instructions include multiple components of desire. And so the intent of my comment was to just ask the question. Because of the way of the assessment is worded, we're unable to tell if all of the elements of desire that are important to women are changing when we see a score change or if just one or two of the components are changing.

So the question to the committee is, if we don't have that specific information, if it may be just one or two of the components of desire that are changing, is that sufficient in terms of benefit?

DR. LEWIS: Thank you. Unfortunately, we are seriously behind time. We're going to have to cut it off after one more question, but we'll try to make time later to address other's questions.

Dr. Curtis?

DR. CURTIS: Kate Curtis. This question is for Dr. Lehrfeld. In thinking about how these strategies might mitigate risk, I'm wondering if you have any evaluation data or examples from other drugs on DDI screening and how well that works to prevent concomitant use of medications? And the same for REMS, do you have evaluation data about REMS and alcohol use for other drugs and how well that works?

DR. LEHRFELD: The drug-drug interaction screening technology that's utilized by pharmacies, it's standard in all pharmacies, that they have to perform drug utilization review, which includes drug-drug interaction screenings.

The success of that -- I mentioned in my presentation there are some limitations when people go to different pharmacies for their two interacting medications and don't use their insurance, which is also screening.

So it's the accepted way of addressing drug-drug interactions with contraindicated

medications in this country.

DR. CURTIS: We don't have any actual data on how well that works on that.

DR. LEHRFELD: No, I don't have any actual data on it. As far as the REMS, I think I'm going to let Claudia Manzo, Dr. Manzo take that.

DR. MANZO: Can you repeat that second question again?

DR. CURTIS: Yes. It's the same question for REMS and alcohol. Do we have any evaluation data or other examples about whether any kind of a REMS would work for mitigating use of alcohol with other drugs where that would be a problem?

DR. MANZO: We don't have a whole lot of REMS specifically designed to address the use of the drug in combination with alcohol with the exception of Xyrem. It's not the same type of adverse event with that. It's an exacerbation of CNS depression with concomitant alcohol.

We don't actually have any data now to suggest -- we just don't have the data that indicates that the education is or is not resulting

in patients adhering to their counseling or recommendations not to use them concomitantly. In fact, we have adverse events that show that they have done that.

DR. LEWIS: Thank you. We are going to have to break for lunch now. We'll reconvene in this room in 45 minutes. We'll cut it short in order to accommodate everyone.

Please return by 12:25 at which time, we'll begin the open public hearing session. Please take your personal belongings with you when you leave. And panel members, I'm going to remind you not to discuss the meeting topic during lunch amongst yourself or with any members of the audience. Thank you.

(Whereupon, at 11:40 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:21 p.m.)

Open Public Hearing

DR. LEWIS: I'd like to reconvene the afternoon session. I'd like to be able to give all of the public hearing people an opportunity to speak, and if possible, a little more time for a couple questions before starting the panel discussion.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of each individual's presentation.

For this reason, FDA encourages you, the open public speaker, at the beginning of your oral statement to advise the committee of any financial relationship you may have with the sponsor, its product, and if known, it's direct competitors.

For example, this financial information may

include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance here today. Likewise FDA encourages you at the beginning of your statement to advise the committee if you do not have any such relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments you provide us can help the agency and this committee in their consideration of the issues before us.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open manner where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chair. Thank you for your consideration.

So each speaker has a limited amount of time, and I'm going to ask that we get started with the process now. So will speaker number 1 please step up to the podium and introduce yourself. Please state your name and any organization you're representing, for the record.

DR. LARKIN: Hi. My name is Dr. Lisa Larkin. I'm from the University of Cincinnati in Cincinnati, Ohio. I have no financial interest in the outcome of this meeting. I do have a profound interest in the outcome as a clinician. I'm honored to be here. Thank you for the opportunity to speak.

I'm here today speaking to you as a clinician and as a patient six months from completion of breast cancer treatments. I'm an internist, a women's health internist. I've been in clinical practice for 25 years, both in an academic and a private setting.

I see patients, lots of patients; 75 to 100 patients a week, most of them women, and I teach residents and medical students. To be sure, I

didn't become an internist with a vision of becoming a female sexual health clinician. It was the unmet sexual health needs of my patients that led me to seek additional training to become in NAMS and ISSWSH and now to direct the UC Health Women's Center and our menopause and sexual health clinic.

What I know as a clinician is that women, real women, many women, my patients, patients across the country, have real and distressing unmet sexual health needs. These women come to me day after day asking for help and looking for solutions. I'm here today because I want to help my patients, and I want there to be options for patients who need help.

It's been established that HSDD is the most common form of female sexual dysfunction. It's real. It causes distress. There's a clear biologic basis, and we have tools to diagnosis this in our office.

I take real issue with those who suggest that low libido in women is always the result of

relationship or situational issues, anxiety or depression, it's something that can always be addressed with psychotherapy, or that pharma has somehow created this disorder as a niche for a drug. If you believe any of those things, I would ask that you come spend a day in my practice and meet the women I care for.

Flibanserin should be approved. It should be approved both because of the data of efficacy and safety, the data that's been shown here today.

Flibanserin should also be approved because there's a profound unmet need for an FDA approved medication for HSTD. That's my personal opinion, of course, based on my understanding of the data, my experience as a primary care provider, and as a breast cancer survivor.

It's also the opinion of a clinician known by her peers to be evidence driven, conservative, cautious, and always a slow adapter of new drugs. Safety of medications I prescribe is my number one concern. I don't jump on the bandwagon of new medicines easily. I've been burned in my career by

postmarketing safety issues. Think Vioxx.

In my community, I'm passionately outspoken and frequently lecture about the potential dangers of unregulated, untested, unproven, compounded medications and supplements frequently used by my patients. I understand the FDA's concern about the safety of flibanserin, and I believe when the data is looked at in totality, flibanserin should be approved.

Flibanserin has known potential side effects, just like every other medication. We heard the data today. No medication is a hundred percent safe. The side effects of flibanserin are largely mild to moderate and are uncommon. And the issue with breast cancer, 9,000 patients studied, no breast cancer in humans. And I must ask if that was an issue for the FDA, why was that not addressed earlier?

In my opinion, the side effects of flibanserin, especially with the risk management options proposed by the sponsor, should not preclude approval. When I prescribe an FDA

approved medication, I'm confident about the dose and purity of the product my patient receives. In addition, I have a PI that clarifies the data, side effects, and potential drug interactions. What an FDA approved medication also does is allow me to discuss risks and benefits with my patients based on solid data and always I discuss risk/benefit with my patients.

I do it when I talk to women about the risk/benefit of daily aspirin for stroke prevention, postmenopausal hormone therapy, coumadin for A-fib, ditropan for OAB, and even chemotherapy for early stage breast cancer. My discussion of risk/benefit for flibanserin with patients would be the same.

As with any other medication, each woman would need to weigh the risk/benefit for them in taking this drug. This is called shared decision-making. It's what clinicians and patients do every day. It's what I do every day. I hope you'll approve flibanserin.

DR. LEWIS: Thank you. Speaker 2?

DR. GOLDSTEIN: My name is Dr. Irwin Goldstein. I serve on Sprout's Advisory Board.

MS. GOLDSTEIN: And I'm Sue Goldstein. We're here for San Diego Sexual Medicine today and we have no financial interest in today's outcome.

DR. GOLDSTEIN: I firmly believe that women have the right to sexual healthcare. I've been a sexual medicine practitioner for almost 40 years. Here I am at beginning of my career. I'm currently director of Sexual Medicine at Alvarado Hospital and clinical professor of Surgery at UCSD.

I've written over 300 peer reviewed publications, and I've more than 20 years of NIH funding in sexual medicine. I provided biopsychosocial management for over 2,000 patients with HSD and distressed by it. Several are here. These women with HSDD have poor life quality, lose relationships, have low self-esteem, and currently have no biologic FDA approved treatments available.

The picture here shows the beginnings of the International Society for the Study of Women's Sexual Health, an international society I helped

found, dedicated to the study and biopsychosocial management of women's sexual health concerns.

This is Sue and me 17 years ago when I was first author on the sildenafil New England Journal of Medicine manuscript. This oral drug for erectile dysfunction was fast-tracked by the FDA in just six months with less than 2,000 patients studied and no AdCom.

The FDA has given men with erectile dysfunction, hypogonadism, and penile curvature, and their providers, choice. Women and their providers are capable of the same kind of risk/benefit discussions. Today for the millions of women with biologic reasons for distressing low desire, we only have off label options with non-documented risks.

Women have the right to sexual healthcare, like the patients with HSD you are hearing from today and like my wife.

MS. GOLDSTEIN: As a sexuality educator, I have shared my story publicly, including yesterday on the hill. I've been married to a world leader

in sexual health for 41 years, but it surprised us both to learn I had HSDD. When I finally realized that my body had betrayed me, I wanted my sex life back. No more avoiding sex or having duty sex.

Women have a right to enjoy sex as much as men. We do not have to accept changes in our bodies. We should have the option for treatment. As a clinical researcher, I've handed tissues to women crying in my office, happy for the temporary treatment while in a clinical trial and sad that the trial was over, ending hope for improvement of their HSDD.

I've seen women convinced that they could not maintain their relationship or would never be able to be in a long term relationship without sexual desire. As an author, I have interviewed women in a relationship, divorced, or single, straight or gay, but universally their sexual problems were wreaking havoc on their lives. Physicians they approached for help assigned the dysfunction to a relation problem, exhaustion, shrugged it off or attempted to treat the

dysfunction, often making it worse. Without FDA approved treatments, practitioners were left with a lack of knowledge. Collectively, I hear a cry for help.

We know that something is changed, and it is not our love for our partners or our relationships. We are seeking a safe and efficacious treatment to bring joy back into the bedroom, our relationships, and our lives. Today we ask that you consider flibanserin with the same requirements of safety and efficacy as you do for men. Allow women to feel whole again. Please give our providers an FDA approved product for the treatment of HSDD.

DR. GOLDSTEIN: To the experts on the AdCom who do not manage women with sexual health problems, give these women the right to choose. Vote yes to approve and thank you.

MS. GOLDSTEIN: Thank you.

DR. LEWIS: Thank you. Speaker 3?

MS. GREENBERG: My name is Sally Greenberg, and I'm executive director for the National Consumers League. I have no financial interest in

the outcome of this meeting. My organization has a long history -- we've been at it since 1899 -- of working for gender equality, especially when it comes to the health of women.

So it's fitting, we think, that the National Consumers League speak out today in support of treatment for a life-altering condition, which causes women a great deal of stress and has a negative impact on their intimate relationships and on the health of their families.

What's of particular concern to me is that today women, because they have no safe or effective FDA approved treatment options for HSDD and out of desperation, turn to the Internet and order online what amounts to snake oil, and dangerous snake oil at that.

I'm talking about the explosion of treatments. Try googling female sex drive, and you'll see what I'm talking about. These scary products are at best costly and ineffective, at worst, downright dangerous.

Let me read a few names to explain what I'm

talking about. Scream Cream, O-Shot, which is a scary vaginal shot of God knows what. Horny Goat Weed, Invigor [ph], Lubedia, KamaSutra, Love SX. FemStim, which is described as an ultra-potent female libido booster scientifically developed, clinically tested, and doctor approved. Femestril, which claims to increase female sexual desire naturally and comes with a money back guarantee. Foria marijuana, which is an infused personal lubricant. It says it's handcrafted from the female flower of the marijuana plant, one of the oldest known aphrodisiacs in the world. Yeah, right up there with oysters and chocolate.

Clearly, there is a huge unmet need for treatment for women's low libido, and yet there is nothing - nothing - proven safe or effective. It's a fallacy to think that women are not being exposed to risk. Today, they're being exposed to a far greater risk than they would if we had an FDA approved drug that is proven safe and effective. The best thing that can happen, of course, is that we get this FDA drug approved and set realistic

expectations for the benefit and potential risks of a therapy that's been thoroughly studied and can be labeled and the company and the drug are held to FDA regulated promotional guidelines.

None of the treatments whose names I read you, and there are many more I could mention, are held to any of these standards. So that's why we got interested in the issue, and since that time, I've met with many, many patients and clinicians who treat women with HSDD every day in their practices.

It's their voices that we have heard loud and clear and that made me understand how important it is that they have access to safe and effective FDA approved treatments. Flibanserin has met every possible criteria, and we want flibanserin and competitors to be available to women because we want women to have those choices.

Just as men have many, many options for male sexual dysfunction, so should women. Thank you for considering this critically important decision for women's health.

DR. LEWIS: Thank you. Speaker 4, please?

MS. WEINSTEIN: Hi. I'm Lori Weinstein and I'm the CEO of Jewish Women International, and I have no financial interest in the outcome of today's hearing. I want to thank FDA for the opportunity to speak today on behalf of the 75,000 members of Jewish Women International who share our belief that female sexual dysfunction has been overlooked for far too long.

JWI is an organization dedicated to empower women and girls. In fact, until recently, I would say that we address the two most important issues that keep women and girls from having full gender parity: physical and sexual violence and income inequality.

But the apparent insistence that female sexual dysfunction has neither a place nor a remedy on the same shelf as male dysfunction reminds us that there is yet another arena where women are voiceless.

For our members who advocate for parity in health, wellness, safety, and security, we see the

disparity in the drug development approval process and post-approval proliferation when it comes to drugs that treat sexual dysfunction. To date, that count is 26 to zero.

Flibanserin has been studied in over 11,000 women for one common condition, hypoactive sexual desire disorder. The data package is one of the largest ever submitted, 10 to 15 times the average for all drugs winning FDA approval. It has consistently met its endpoints in its pivotal trials.

Simply put, women in the trials found the drug to increase their desire, decrease their distress, and bolster the number of satisfying sexual events. Minimal side effects, but results that clearly indicate the potential to restore self-esteem, rejuvenate a deteriorated sexual relationship with an intimate partner, and create happy couples, which undergird happy families.

More importantly, the drug has shown a modest, but significant improvement with minimal side effects. As with other drugs, the doctors

that prescribe them and the patients that take them, we surely can trust women with HSDD and their healthcare practitioners who advise them to decide if this is in fact the right medication for them.

For those for whom flibanserin doesn't work, we need to give women and their doctors the credit that they need, the credit that they deserve, that they in fact will terminate use.

JWI as a women's organization is deeply concerned about healthy women, quality marriage, and thriving families. Flibanserin, if approved, will go a long way to restoring self-esteem, healthy sex, and loving relationships that have been undermined by HSDD.

We believe the science is there for the approval of the drug. Approval, in turn, provides an important step towards opening a pipeline of investment, research, and discovery to fortify the availability of new and effective treatments for HSDD for both pre- and postmenopausal women.

If not approved, we fear the pipeline of drug development for what FDA recognizes is an

unmet need will go dry. Again, I thank you for the opportunity to speak today.

DR. LEWIS: Thank you. Speaker 5, please?

MS. SCANLAN: Good afternoon. My name is Susan Scanlan. I have received a consulting fee from an organization supported by Sprout Pharmaceuticals, but have no financial interest in the outcome of this meeting.

I've dedicated my life and career to achieving progress for women across all aspects of our society; first, as chair of the National Council of Women's Organizations, and now as chair of the Even the Score Coalition.

What I've learned from 40 years of championing women's rights is simple. Progress, at its foundation, at its very core, is about people. It's about making life better for people. That's why I'm here today, and it's why I hope all of you are too.

I'm here to stand for progress for the millions of American women living with HSDD. I'm here to stand for progress for those amazingly

brave women and their partners who have come today to tell their very personal stories of struggle and heartache, in hope of a solution from all of you.

Sexual intimacy is one of the most private parts of our lives. For women to courageously open the door to their bedrooms and speak publicly of their own battles with sexual dysfunction, underscores just how much they value a healthy and pleasurable sexual life.

Progress in this case comes down to respecting a woman's right to make her own decision as to the best path for achieving her best sexual self, whatever that may be. Let's call it the pursuit of happiness; a pretty longstanding right in the United States of America.

It's why we created Even the Score, and it's why two dozen well-known and well-respected women's rights and health organizations stand with me today, ready to support you, ready to support the FDA, as you prepare to make history, or shall we say "herstory," by acting for women and approving the first ever medical treatment option for HSDD.

Thank you.

DR. LEWIS: Thank you. Next speaker, please?

DR. KRYCHMAN: Hi. My name is Michael Krychman. I'm a sexual medicine gynecologist, certified sex therapist, and AASECT sexual counselor. I have no financial disclosures on the outcome of this meeting. I stand before you as the 2013 Women's Initiative in Sexual Health or WISH award recipient for excellence in sexual health.

I represent thousands of men and women, therapists, healthcare professionals, and patients who are committed to bring their voice and their wish to the FDA today to be heard.

As Margaret Mead once said, "Never underestimate the power of a small committed group of individuals to change the world. Indeed, it is the only thing that ever has."

Please watch and listen to only but a few of their important messages.

(Video played.)

Thank you.

DR. LEWIS: Thank you. Speaker 7, please?

MR. SHIELDS: Good afternoon, everyone. My name is Wayne Shields. I'm president and CEO of the Association of Reproductive Health Professionals. And thank you for making this time available for so many of us to speak. Really appreciate it. I also want to personally and professionally thank you for your due diligence on this process. I think it's been very important, and it's led us to a good point right now.

I wanted to talk a little about ARHP professionally, and then I wanted to end with just a little bit of personal insight on this.

About ARHP, ARHP is a national medical society. It's a membership group. Our members are all members of the healthcare team. They're doctors, nurses, nurse practitioners, PA's, also educators, sex counselors and therapists, and it's an education organization, and what we do for a living is education. We do certified education, and we focus on sexual health. So this is of central import to the 12,000 members of my

organization.

If we could go to the next slide? Thank you. Just quickly, I wanted to show the variety of folks who I represent here. I'm just one person, but I represent 12,000 professionals who come from all disciplines and practices. So this is a nice breakdown. You can see there are doctors, nurses, and PAs, but researchers and educators, too, primarily in sexual and reproductive health.

We're also -- my folks, the people I represent, practice in all healthcare sectors. And in every one of these healthcare sectors, our folks, my people, interact with, provide counseling for, and work to provide patient-centered care for women who have HSDD. So this is an important issue to us.

We also have a great number of specialties in our organization, and the point of this is to show there are a lot of healthcare providers who deal with this issue. It's not just the sexuality focused counselors. It is all members of primary care and of specialty care. The world is changing,

so this care is very important to focus on.

This final slide is for you to see who advises me. This is my leadership. They told me, their CEO, what it is that they support. And all of us in the organization, the leadership, the staff, all of our committees, support the approval of this important medication to add to the toolkit of treating HSDD.

It's very, very important that you all hear that my organization and the professionals that tell me their positions, that they highly support the process you've gone through. Your due diligence has been amazing, and it has been really important to bring this conversation to the forefront.

But let me also say that HSDD is real and that flibanserin is an important option. We support the approval of flibanserin, as an organization, my 12,000 people support this, so we hope that you will leave with a positive finding. I think also on a personal note, I just want to say, I'm also a feminist. See me in the corner

there; I'm always the only guy in the room pretty much. And also I support concepts like choice; and I support individual rights; and I support the strength of individuals being able to make decisions and being smart enough to understand risks; and I support the provider/patient dynamic. It's very important.

So let's go ahead and approve this medication, and let's make it a choice for those folks who deserve this option. Please approve flibanserin.

DR. LEWIS: Thank you. Speaker 8, please?

MR. SHIELDS: Oh, I didn't give my financial disclosures. I have no disclosures.

DR. CLAYTON: I'm Dr. Anita Clayton, chair of psychiatry and neurobehavioral sciences at the University of Virginia School of Medicine. I am a consultant to Sprout and have worked with researching flibanserin for more than a decade, along with numerous other CNS active drugs already on the market or in development. I anticipate no personal benefit from the outcome of this meeting,

and I have no promotional marketing relationships with any company to disclose.

I was here in 2010 and presented on flibanserin to the first AdCom. Just one year ago, I boarded a bus with the leaders of 10 women's advocacy organizations to talk to the FDA about our frustration. In that meeting, the FDA acknowledged that unconscious gender bias may be impacting this process. Because of the time constraints, I'm going to get straight to the point.

Stop moving the goal posts. The efficacy, safety, and clinically meaningful effects of flibanserin are clear, but now the FDA's briefing book states that hypotension syncope is the most concerning adverse event with flibanserin.

Think about that. We're not talking about heart attacks or death as we did with the PDE5 inhibitors or seizures when bupropion or Wellbutrin was approved. We're talking about a rare risk, a "rare" risk of decreased blood pressure that in the worst case results in fainting.

If your vote today is no based on this risk,

it would signal that you don't believe that HSDD warrants treatment at all. It would signal that you are going to paternalistically decide that a drug with benefits that are meaningful to patients should be withheld because you're worried that on an extremely rare occasion someone may faint.

Maybe the message is that you don't trust women with HSDD not to drink to intoxication or you just don't trust women. You cannot send that message. Not to the courageous women who spoke in October and will speak today, nor to the women who are watching the actions of this committee before they speak.

As a woman and as a physician who spent her career helping women with their sexual issues, I can't imagine what that message would convey. I was here in 2010. It's been five years. Approve flibanserin today. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 9, please?

MS. BATTAGLINO: Hello. I'm Beth Battaglino, president and CEO of healthywomen.org.

I've no financial interests in the outcome of this meeting. As the nation's leading information source for women, I'm here to represent more than 5 million women who come to us looking for answers to their most pressing health concerns.

Today, we have an opportunity to write a new chapter, and I stand to support as the FDA acts for women and recommends approval for the first ever medical treatment option for female sexual desire disorder.

I asked to speak so that I can share some real-world insights that further support the fact that HSDD is a key unmet medical need for women. In September, 2014, HealthyWomen conducted a medically-vetted survey on the topic of women's sexual desire. In less than two weeks we had over 500 women responding to this survey, ages 20 to 60 years old who said they had low sexual desire and felt distressed because of it.

The survey results speak for themselves. When asked to rate their distress on a scale of 1 to 7, over 60 percent of the women said they had

considerable distress. The majority of the women, 90 percent, said they would like to have more desire or have sex more often. In fact, over 70 percent of the women said that their low sexual desire had caused personal problems for them.

The most revealing insight that our survey uncovered was the awareness of their situation as a medical condition was fairly low; 72 percent of premenopausal and 60 percent of postmenopausal women did not know that low sexual desire accompanied by distress was treatable.

These survey results add to the evolving recognition of the importance of sexual functioning in women's lives. We know firsthand that women do struggle with issues related to sexual health. Women deserve the safety and peace of mind that comes with access to FDA approved medical treatment for HSDD. Thank you.

DR. LEWIS: Thank you. Speaker 10, please?

MS. PARRISH: I'm Amanda Parrish. I'm one of the lucky 11,000 women that was a patient on the flibanserin clinical trial. I'm here with my

husband, Ben. We funded our own trip, and we have no financial stake at the outcome of this meeting.

Yesterday, I had the privilege of spending the day on Capitol Hill discussing the importance of treatment options for HSDD. Ten years ago, I was blessed to meet my husband, Ben, and I am grateful that he is here is support of me and anyone who's experienced the devastating effects of HSDD.

Having both experienced failed first marriages, we came together with intense chemistry, passion, and a determination to handle our new found love with TLC. What neither of us expected was the abrupt and total disappearance of my libido and desire for sex.

Having both been active initiators, we were totally unprepared when my desire for sex suddenly left the building like Elvis' blue suede shoes. Not like it temporarily left when I had four small kids or when my father died. A silent wall of shame grew between us, shame of guilt on my part for not wanting to have sex with a man whom I

loved, and hurt on his part wondering what he was doing wrong. Often pretending to be asleep before he came to bed, we suffered separately in silence, seriously threatening our relationship.

I was fortunate to be enrolled in the clinical trial for flibanserin and what a relationship saving eight months that was. As if the light switch had been turned on, so was I. Once again sexually confident, I returned to the flirty and initiating woman Ben fell in love with. The trial stopped leaving me with no medical option, and life returned to uncertainty and distress.

I purchased some voodoo medicine promising restored libido, but was too frightened to take it knowing that you, the FDA, had not approved it, and a prescription for off-label testosterone proved completely ineffective, and the side effects frightened me.

Luckily Ben is a prince. Others are not so lucky as I hear from men every day who believe their former spouses suffered from HSDD. Former is

the operative word. Could their relationship have been saved? No one can know.

What I know is that flibanserin taken each night worked for me and worked for my marriage. I fully understand the importance of weighing risks and benefits of any prescription drug and know that no drug is without risks or side effects, even Tylenol. But I should be able to determine with my physician if the risks of flibanserin are worth the benefit of treatment, and for me, the effects were not modest, but significant and the side effects non-existent.

For the record, I am a woman, not a mouse. I would not take four times the intended dose, and quite frankly I was offended that this would be compared to a date rape drug. I love sex with my husband, but if I don't have the desire to have sex, I will either opt out or simply oblige, which shortchanges us both. Much like even though I love steak, I'm not going to eat one if I'm not hungry.

I want to want my husband. It is that simple. I implore you to approve flibanserin,

understanding that although it may not work for everyone, it certainly worked for me and thousands of other women. For us, flibanserin is a lifesaving, relationship saving, and life changing drug. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 11, please?

MS. CAMPBELL: Hi. My name is Katherine Campbell. My travel expenses are being reimbursed by Sprout. I hope everyone understands that my husband and I do not have money set aside to fly back and forth to DC so that I can talk about how much sex we're not having.

I have no hidden motives or agendas, and I was not even on the clinical trial. I'm simply an intelligent, fully-grown woman who knows her body better than anyone else, even my doctor. A television doctor suggested on an interview just last night that maybe my libido is low sometimes, because I've had a bad day. An anchor on a morning show yesterday said that she doesn't need treatment because a housekeeper and time away from the kids

would solve her desire issues.

If your sexual desire issues can be cured with a good day and a babysitter, then congratulations, you do not have HSDD. But the rest of us would sure appreciate it you would stop dismissing our concerns and making a complete mockery of the issue. If I sound frustrated, it's because I am.

Today's my son's first birthday, and I'm missing it because I'm here desperately looking for help to recover what I've lost, a vital and beautiful part of my marriage. I'm struggling to find the right words to describe how painful this journey has been for me, and then I realize it's not just about me. It's about the millions of other women I have to represent today who are looking to the FDA for a solution.

These are smart, modern women who are a hundred percent capable of knowing their own bodies and making good decisions. We want and deserve options. I was not on the clinical trial for this drug, but I hear the concerns about the side

effects. It feels like a slap in the face. I'm basically being told that I'm not smart enough to stop taking something if it isn't working or if the side effects are unbearable. And honestly, I have most of these side effects after taking a vitamin on an empty stomach.

The critics say the improvements might only be modest, but oh, what I would give for even a modest improvement. I do understand the numbers and statistics. This will not be a miracle drug, and it won't turn me into a sex addict, but maybe I'll think about sex. Maybe I'll have a fantasy again. Maybe I'll even flirt with my husband a little bit.

As a woman who truly has HSDD, is premenopausal, is in a committed relationship, and is in complete distress, I am pleading for help for an option. And when you hear me, I hope you see not just me, but all the women this disorder is hurting. Thank you for listening.

(Applause.)

DR. LEWIS: Thank you. Speaker 12, please?

MS. BARCLAY: Good afternoon, and I have no financial disclosures. So I'm Lynn Barclay, the president of the American Sexual Health Association. Our organization was founded more than 100 years ago. In that century of working in sexual health, it's been apparent from the early days that there is seldom a one-size-fits-all answer to the many challenges real people face in achieving and maintaining sexual health and satisfying sex lives.

What works well for one may not be nearly enough for another. So the best approach is often an array of solutions that are as diverse as the populations we serve. We firmly believe that this is the case with women, just like me, who are struggling with issues of sexual desire.

Let's face it. This is a complex issue. Sexual desire is an interesting brew of mind and body with a dash of society and a pinch of interpersonal issues tossed in. For some women, these matters are best addressed with a bottle of champagne, a romantic stroll on a beach, or good

therapy. Other women need something else, maybe a combination of things.

What makes me sad, worried, and to be honest, annoyed, is that there are no medical options available for women for whom biological factors are at play, not one. We've said that many times today, this condition that FDA itself recognizes is a top unmet medical need in the U.S.

Our organization believes sexual health should not be seen as separate from our overall health. Each impacts the other. Sexual health is, in our view, not a privilege, but a right. We believe both men and women, as well as their healthcare providers, should have choices in addressing sexual dysfunction. We also believe that women and men can be trusted to decide for themselves about using an FDA approved and healthcare provider prescribed treatment option.

We applaud you for this focus on women's sexual health, which really is the focus on women's health. This is about a woman's wellbeing, her quality of life, and you better believe it affects

her partner, too. You've heard the saying, "If mama ain't happy, ain't nobody happy."

(Laughter.)

MS. BARCLAY: Well, as grammatically imperfect as that may be, it makes a good point. Let's make sure mamas, grandmas, aunts, sisters, and women just like me everywhere, have a complete menu of choices. We deserve it, we are worth it, and in the end, we will all -- all -- be better for it. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 13, please?

MS. REID-HAFF: Hello, my name is Judith Reid-Haff. My expenses are being reimbursed by Sprout. I have no financial interest in the outcome of this meeting, but I am hoping to have a better sex life.

As I said, my name is Judith. I'm 67 years old. I was here in October giving my story to the FDA, and once again I return as I have been struggling with HSDD for 17 years. I'm interested in the unmet needs of women.

It is not solely the woman who is affected by this disorder, but her spouse, significant other, children, people in her social circles and workplace, all of which I have firsthand experience. It is crucial that we get help.

I'm a breast cancer survivor twice. The second time in 2010, I had a bilateral mastectomy and was taken off estrogen. The results were disastrous, zero libido, libido intense pain with intercourse, hot flashes resulting in 45 minutes cumulative sleep per night, and fierce mood swings.

In the past three years I've been on DHEA, progesterone, estradiol cream, EstroGel, and Testim. These medications have eliminated 75 percent of my previous problems and improved my quality of life maybe a hundred percent. However, HSDD is still prevalent, and I want a safe and effective treatment.

Healthy sex to me is like sleeping and eating. It's part of a great life. HSDD, since it affects most, if not all women, interface with society in general and her family in particular, in

a very serious disorder and negatively impacts a broad spectrum of humanity. Any and all solutions or partial solutions to this largely ignored malady will, like the high tide, lift all boats. I would like the opportunity to take flibanserin. Please approve it. Thank you for your time.

(Applause.)

DR. LEWIS: Thank you. Speaker 14, please?

MS. GATTUSO: Good afternoon. My name is Barbara. I'm a nurse. This is my daughter, Vicki. And we are patients of Dr. Goldstein, and we have no interest in the outcome of this meeting, other than as the other gal said, to hopefully get treatment.

Sex is a very, very important part of any healthy marriage. When I lost all desire for sex about 25 years ago, I was devastated. I had a wonderful loving husband and no sexual feelings whatsoever. Our relationship became strained over the years because my continued avoidance of sex.

Attempting over the years to find a solution was frustrating because my doctors had no answers

for me. Finally, in 2011 during a clinical trial for flibanserin, I was diagnosed with HSDD. I was so relieved to know that this is not my fault.

On flibanserin, the change in me was dramatic. My desire returned to a level I had not seen in all those years and also had no negative side effects, only positive ones, really good ones. Sadly, the study was discontinued, and without the drug, all those wonderful feelings ceased. For myself, my daughter, this can be a hereditary problem, genetic, and countless women suffering from low sexual desire.

I implore the FDA to approve flibanserin and give women and their physicians a choice to make an informed decision. Thank you.

MS. LOFTHUS: Hi. My name is Vicki Lofthus. I was on the patient panel in October 2014 and told my story about how HSDD has negatively affected my life. My mother was on the panel as well. We've all shared our individual struggles, which were sadly very similar. I have two young daughters, and it scares me to death to think that one day

they could get this disease.

Since my appearance on the panel my marriage has suffered greatly, so much so that the conversation of divorce is on the table, stemming from my low sexual desire. My husband has a difficult time understanding my struggle with this disorder. He still takes my avoidance of sex personally, thinking I don't love him anymore and there is something wrong with him, which is farthest from the truth.

Out of desperation, I recently went as far as trying a new testosterone treatment that is on the market for men, and the side effects were negative, including breakage and thinning of my hair along with facial hair growth.

I currently continue to use it because it is my only option right now, and for me, the minimal benefits outweigh the unpleasant side effects. I know that flibanserin will help countless women struggling with low sexual desire.

All women that are struggling with HSDD should have the option to choose a safe and

approved treatment with guidance from their healthcare provider. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 15, please?

MR. GATTUSO: Hi. My name is Greg Gattuso. My expenses were paid by Sprout, but I have no financial interest in the outcome. You just heard from my wife and daughter. My wife, Barbara, has HSDD. I know that now, but for the past 25 years, her desire for sex was non-existent, and I didn't know what was wrong.

Was it me? Was she having an affair, or suspect me of having one? The answer to both those questions is no. But it put a strain on our relationship, and if our love of each other and our children was not so strong, our marriage might have ended.

Barbara was trying to get help from various doctors, but nothing she tried worked. That is until 2011 when she participated in a clinical trial for flibanserin. After being on the placebo for seven months to no effect, she was given the

real flibanserin.

The results were amazing. Her desire and passion returned but only for a short time. Well, the study was discontinued, and without the drug, her HSDD returned. While on the drug, she suffered no side effects. My daughter was also diagnosed with HSDD in her mid-30s. I fear that with nowhere to turn, she could face what her mother went through; decades of loss of intimacy and subsequent strain on her marriage.

I'm diabetic and one of the side effects is erectile dysfunction. I however, have numerous options available to treat this disorder. I'm aware of the possible side effects and as with most men, suffer none of them.

I urge the FDA to allow patients and their clinicians to make an intelligent, informed choice to take flibanserin, weighing their individual benefits against the seemingly mild side effects. Please pass this medication. Give my wife and daughter a choice.

(Applause.)

DR. LEWIS: Thank you. Speaker 16, please?

MS. JOHNSON: My name is Gay Johnson, and I have no financial disclosures. I'm the CEO of the National Association of Nurse Practitioners in Women's Health, and I would like to thank the FDA for the opportunity to speak on behalf the membership of NPWH and the women they serve.

Our mission is to ensure quality healthcare to women of all ages. Sexual health is a significant component of wellness for both men and women, and quality healthcare includes managing sexual health problems.

Our members are at the front line of this issue caring for women with HSDD in their practices every day, and they do not have any FDA approved options to provide relief to those patients. Women's sexual health is complex and multidimensional and often overlooked in primary care due to many factors, including cultural conditioning of women and providers where historically women's sexuality has been viewed as something tied to the obligation to have sexual

relations for reproduction, but not the desire to have sexual relations to achieve personal pleasure.

Thankfully, now in the 21st century, women's sexual health is seen as a valid component of overall wellness. Women's sexual dysfunction is now recognized as a real medical condition of real women that decreases the quality of life and negatively impacts relationships.

NPWH is dedicated to lifelong learning. Our members frequently request female sexual dysfunction as a topic for education and training because the condition is frequently identified during well woman visits, and knowledge of treatment options is often not taught in depth during basic education.

Due to this demand, NPWH developed and implemented the first women's sexual health course for nurse practitioners in 2014. The demand was intense, and the course was filled to capacity weeks before the program began. We're repeating this course this year, and again the course has filled to capacity.

Each HSDD medical treatment option should receive fair consideration, and the side effect adverse event profile evaluated while considering the significant impact of the condition. Women are intelligent, insightful decision makers and can be trusted to evaluate the risk of side effects, adverse events, and benefits of any treatment according the impact of HSDD on their personal life and relationship.

We applaud the FDA for recognizing female sexual dysfunction is a key unmet medical need, and we look forward to standing in support as the FDA acts for women and recommends approval of the first ever medical treatment option for women's most common sexual complaint. I would also like to add that our colleagues of the American College of Nurse Midwives join us in support of our statement. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 17, please?

MS. STOUP: My name is Kelli Stoup, and I have no financial things to disclose, but I will

disclose the fact that I'm a bit scared to death to stand up here and talk about this. I do thank you for the opportunity to speak today.

As I said, my name is Kelli Stoup, and I've been married for 17 years, and I have two children. I am here today to represent myself, some of my friends, and thousands of other women who are not able to be here today.

You don't know me, but I'm a very private person. To stand up here in front of a room full of people who are looking at everything that I do and everything that I say, and to tell them that I am broken and cannot be fixed, that I could go without sex for the rest of my life, that I have zero interest in sex, is humiliating, depressing, and causes great anxiety and distress in both myself and my marriage. I am a private person, but I am willing to stand here and speak about this. I am passionate about this and willing to speak on behalf of those who cannot be here.

Years ago when I asked my OBGYN about my low libido, I was told I would just have to figure out

a way to get in the mood. A few years later, I asked for help again from another OBGYN. My words were "You have to help me. I never want to have sex. I have no libido, and it's killing my marriage. It is so stressful. Please help me."

This time I was advised to try compounded testosterone. That didn't work. Other options that were offered were testosterone troches that you stuck under your tongue, and vaginal suppositories, which at that point I declined.

Finally, after seeing a urologist whose specialty is sexual dysfunction, I was diagnosed with HSDD. I have tried several additional options of therapy, including Testim Gel and Wellbutrin. On the testosterone, I was neurotic about growing facial hair, which by the way did not increase my libido. The Wellbutrin did make me a happier more even keeled mom, one bonus, but no libido increase. So my children may thank you for that, but my husband still did not thank.

At this point, I have given up. I am only willing to submit my body to so many products that

are really not indicated for this problem, whose results are a crapshoot at best and some with pretty nasty side effects.

Not only does it cause distress for me, it has caused strife in my marriage. My husband knows I love him, but he continually feels rejected and knows when we do have sex, it's because I know he needs it and is what a husband and wife should want to do. I continually go back to the old line "It's not you, it's me."

Let's not kid ourselves. We are not curing cancer here, but we do have to understand it is a real problem that many women and their partners have to deal with every day. I have never tried flibanserin, and it may not even work for me.

That's the way it is with any drug the FDA approves. It may not be for everyone or work for everyone. I will need to figure that out with my doctor. All I ask is that when a woman like myself gets up the courage to go to a doctor and admit that she is broken, that it is affecting herself, her marriage and her self-esteem, and she needs

help, that there's at least one FDA approved option that she can be given to try. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 18, please?

MS. PEARSON: Hi. I'm Cindy Pearson. I'm the executive director of the National Women's Health Network. The network does not accept any financial support from the pharmaceutical industry or medical device manufacturers.

Like the other speakers today, we also recognize that lack of sexual desire can be a distressing problem for women, and like other speakers, we do believe that it might be possible to develop a drug that is effective for some of women's sexual problems. However, we disagree that flibanserin is that drug.

Now, you've heard some women already, just here, talk about, to ask, that you recommend that the FDA approve flibanserin, and it is obviously so meaningful to them, it seems just plain mean to say no, but need does not create proof. Nor does the existence of untested and unapproved products mean

that the appropriate response is for the FDA to approve something, anything.

Your task is to advise the agency on the proof that exists about effectiveness and safety, whether enough information is known for women to make a good choice. We think Sprout has fallen short on all of these things. Yes, there's statistical significance, but it's slight and it's unclear how clinically meaningful it is overall, which is what you're tasked with doing, looking at the overall data.

On safety, the incidence of mammary tumors is concerning. The clinical data in women clearly showed the increased likelihood of low blood pressure, fainting, and other potentially serious events. Sprout now recommends taking the drug at night, but altering the timing of the dose doesn't make those dangers go away.

Women also really deserve to know about the interaction of alcohol and flibanserin, and they don’t right now. Sprout claims that the reason they don't is that it was really hard to recruit

women who drink alcohol to be in a study. Talk about gender bias in research. The reality is that for the purposes of an evidence-based assessment of risk to women of drinking alcohol while taking flibanserin, the study has not been done.

We at the network agree with the speakers who've said, "Give women a choice. Trust women to make good choices. Women can weigh the risks and benefits." Women absolutely can make good choices if they have good information. Sprout has not provided enough data for women to make informed decisions. The questions regarding alcohol use, nighttime dosing, drug-drug interactions, cannot be left unanswered.

We recommend that the committee vote no on approving this drug without further studies. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 19, please?

DR. STREICHER: I'm Dr. Lauren Streicher, an associate clinical professor of Obstetrics and Gynecology at Northwestern University in Chicago,

and I have no financial interests in the outcome of today's proceedings.

We're all aware that there's a movement that asserts that sexual dysfunction in women does not exist, but is in fact a normal experience made medical by profit motivated pharmaceutical companies.

The notion that pain and inability to have an orgasm and loss of libido are not real conditions, but are manufactured so that pharmaceutical companies can sell drugs is clearly entertained by people who never have spent time in my office.

Not to mention, they give pharmaceutical companies way too much credit. Female sexual problems have been recognized by the medical community as specific conditions for over 30 years, long before pharma entered the picture of what happens in people's bedrooms. HSDD is not the pharmaceutical equivalent of a Hallmark holiday manufactured to sell greeting cards, any more than Viagra was developed to treat fake erectile

dysfunction.

The scientific presentations this morning have made it clear that an intact libido depends not only on interpersonal influences, but of intact biology as well. Most of the ingredients in the biological libido cocktail includes the physical ability to have a healthy response, hormones, and also dopamine and serotonin, that together determine how often women think about and desire sex.

Dopamine, of course, creates that feeling of "I want sex, I need sex, I can't stop thinking about sex." Serotonin is about keeping desire under control so you stop making love long enough to go to work, do the laundry, and serve on FDA panels.

Flibanserin will not help, and I will not prescribe it for the woman who has a dysfunctional relationship, painful intercourse, or hormonal imbalance. Flibanserin will help my patients who have no libido in spite of a healthy relationship and intact anatomy.

I've reviewed the clinical trials. Taken as directed, there are no serious side effects and sexual desire increased in a meaningful way. I practice evidence-based medicine. And in the case of flibanserin, the evidence is solid.

Sexual health problems are real and deserving of research and development of not only this, but other new drugs. Flibanserin will not solve every sexual problem, but it will treat low sexual desire in a meaningful way and make a difference for millions of women.

I see these women in my office every day, and I will not insult them by recommending talk therapy for a biological imbalance. This drug should not be held to a higher standard than other FDA approved drugs. I look forward to the opportunity to partner with my patients and treat what is a very distressing condition and trust that the FDA will make the right decision.

(Applause.)

DR. LEWIS: Thank you. Speaker 20, please?

DR. FUGH-BERMAN: Good afternoon. I'm

Adriane Fugh-Berman, director of Farmed Out at Georgetown University Medical Center. We have no conflicts of interest on flibanserin or with any industry. I am a paid expert witness in litigation regarding pharmaceutical marketing practices on other drugs.

Thank you to the FDA and to previous advisory committees for protecting women's health by keeping flibanserin off the market. The maximal benefit this drug has is minimal; the benefit of this drug appears to be eight satisfying sexual events a year.

About half the women in flibanserin trials were on oral contraceptives, which can lower libido. So can antidepressants. So can antipsychotics. So can antihypertensives. Discontinuing problematic drugs can be a cure for some women. So can therapy, which Sprout has revealed today has been tried by a vanishingly small number of women in their studies.

Flibanserin is a mediocre aphrodisiac with scary side effects. It doesn't treat sexual

dysfunction. It does nothing for painful sex, nothing for inorgasmia, and it has a trivial effect on libido. Its effects may be due to non-specific sedating effects, apparently equivalent to four drinks.

There's a growing body of safety concerns in a highly selected population of young, healthy volunteers, the population least likely to experience adverse events. Make no mistake, this drug will be widely used off label if it's approved, in menopausal women, in women with concomitant illnesses, women on different drugs. There will be an epidemic of adverse events that will dwarf what has already been seen in these trials.

Boehringer-Ingelheim did the right thing by abandoning this drug in 2010. Unfortunately, it is now in the hands of a company more skilled in marketing than science, and one that has a history of illegal drug promotion.

Sprout's prior incarnation was Slate Pharmaceuticals, infamous for selling its only

drug, testosterone, Testopel, off label, prompting a warning letter from the FDA for many unsubstantiated claims. Sprout's Even the Score campaign is a brilliant marketing strategy that pressures the FDA and gets around laws preventing promotion of drugs prior to regulatory approval.

Is this a company that will market any drug responsibly? To approve this drug would set the worst kind of precedent, that companies that spend enough money can force the FDA to approve useless or dangerous drugs.

MS. HIRSCH: I'm Alessandra Hirsch, project manager at Farmed Out. In three months, I begin medical school, and I hope to be a doctor who prescribes based on science and not marketing.

Flibanserin is intended to be used for premenopausal women like me. But flibanserin must be taken every day, and both alcohol and the birth control pill seriously increase the likelihood of an adverse event. Seventeen percent of premenopausal women are on the pill, more than half of women consume alcohol, so I was surprised to

read that Sprout Pharmaceuticals had trouble finding more than two female subjects for its alcohol study.

This drug has implications for young women that go beyond the physical. Young women don't need another reason not to talk about sex. They deserve encouragement in talking about their needs and communicating with their partners.

Couples should talk about and negotiate disparate levels of libido in the same way they do other issues. Such conversations, essential to women's rights and safety, ensure that we are in relationships where it's okay for a woman not to have sex when she doesn't want to.

Labeling women as abnormal when there is no such thing as an abnormal level of desire and substituting medication for conversation is not what young women need.

Decisions on drug approval should be based on safety and efficacy, not capitulation to an aggressive and unethical stealth marketing campaign. Many of the others you've heard from

today may not have a financial interest in the outcome of this meeting, but I don't think that means that they aren't paid by industry to be here.

We want to thank the FDA for holding drugs for men and women to same high standard, and we implore this committee to reject flibanserin and by doing so, stand up for the FDA, science-based regulation, and women's health. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 21, please?

DR. WOLFE: I'm Sid Wolfe, the Public Citizen's Health Research Group. I don't have any financial conflict of interest.

I think one way of describing the purpose of the meeting today for the advisory committee and for the FDA, is there any difference in improvement and effectiveness or change in safety that would have a different outcome than almost five years ago when the advisory committee here voted 11 to no -- 11 to zero that the benefits did not outweigh the risks.

It was interesting that -- these are just some quotes, direct quotes from people on the

advisory committee at the meeting. And there were several themes which you can see in several of the comments. One, because of the long list of drugs excluded, they wondered about the generalizability of it and the safety issues that you were missing because people weren't allowed to take drugs that could interact.

They were also concerned about the minimal level of effectiveness. The company, as has been discussed a couple times, rejected what they had agreed upon as their primary co-endpoint, which was a daily diary because that diary didn't show any effect and they then went, in the next study, the 174, for the FSFI scale, which did show something, in fact. Changing this kind of important horse midstream is not a good idea.

But because of these concerns that were raised, the FDA took them very seriously. The FDA had some of the same concerns and asked the company to do a number of further studies to try and get more evidence on both the efficacy side and the safety side.

Now, it is the FDA's hope that in 147, the third of these randomized trials, that instead of using as the primary outcome the daily diary, the company, quote, "requested to use another instrument, FSFI, to assess desire after the analysis of their first phase 3 study indicated that eDiary desire was not significantly improved."

But another interesting thing about this study, again this is 147, is that, as you heard this morning, they decreased the number of drugs excluded. There were still a number of drugs excluded. And what you can see here in just the somnolence is that the data from 2010, the two randomized studies then, showed 2.9 percent incidence of somnolence with placebo, 9.5 with flibanserin. But when you then took away some of the drugs that had been excluded before, it went up to 14.4 percent, a significant increase with the placebo effect staying pretty much the same.

As the FDA has stated, hypotension and syncope, unlike the trivial thing that some people have referred to it as, is associated with

flibanserin alone, or when used concomitantly with alcohol is clinically significant and can result in serious, irreversible, or life-threatening injuries. And in the interaction studies, which we've seen, that became clear that there was increase in orthostatic hypotension, syncope, and somnolence.

So the final thing to talk about is the benefit/risk balancing. If there were clear evidence of a clinically meaningful benefit, which I don't believe there is, significant but not clinically meaningful, accompanied by manageable risk, approval might be appropriate, but neither of these two is the case. The placebo-adjusted benefits, though statistically significant, have questionable clinical meaning, as many have described the FDA.

Further, the FDA concluded that even with the most restrictive REMS, it may be limited in effectively mitigating the risk of hypotension and syncope alone and when used concomitantly with alcohol in the postmarketing study. In other

words, they're saying there's really no kind of risk management that would be effective.

So I again urge this committee, augmented with the drug safety and risk management committee, which I was proud to be a member of for four years, to reject the drug. It isn't ready for primetime. As one of the members suggested this morning, there will be hundreds of cases of syncope, and this is not a benign problem when many people can die from it. Thank you.

DR. LEWIS: Thank you. Speaker 22, please.

DR. SILCOX: Hello. My name is Dr. Christina Silcox. I have a PhD in medical physics from MIT, and I'm a senior fellow at the National Center for Health Research. Our research center scrutinizes scientific and medical data and explains the results to patients and providers. These are the perspectives I bring with me today. We do not accept funding from drug companies, so I have no conflicts of interest.

The center strongly supports research to find effective treatments for women who want to

increase their libido, but based on the study results available today, we conclude that the benefits of this drug do not outweigh the risks. We ask you to vote against approval of this drug.

There may be a small positive effect on desire, the distress women feel, and the number of SSEs per month. But with so little benefit compared to the strong placebo effect, is flibanserin safe enough to justify approval? We say no.

First, because the drug was studied only on very healthy, premenopausal women, generally for less than a year of continuous use, but will be taken much longer if it's effective.

The data from these studies show that taking flibanserin increases the risk of low blood pressure, fainting and other potentially serious adverse events. This risk is increased when women are on hormonal birth control. The high dropout rate from adverse reactions to the drugs adds to these concerns. In addition, we can't know the risks for women already taking a long list of

common medications because they were excluded from all three pivotal trials.

Second, because the study shows a dangerous interaction with alcohol for men, but we don't know the risks for women because the alcohol study only included two women for a drug that will only be taken by women, by a company that claims to champion women.

Alcohol metabolism differs for men and women and decreases dramatically right after ovulation. Sprout should have studied the impact of alcohol use on a large group of women. Since they didn't, we don't know the risks, but they will likely be higher than they are for men.

Third, equally important, what are the risks for developing breast cancer while taking flibanserin year after year? The risk of mammary gland tumors in mice increased with dosage, which experts consider an important safety risk, especially at levels well below 100 times the human dose.

This suggests a link to cancer, but the

company chose the wrong mouse strain to study and that makes this data difficult to interpret. But when you consider the mouse data, as well as the genotoxicity results in one of the in vitro tests, there are too many red flags to ignore. Sprout should repeat the study again with a mouse strain that has a lower and more predictable baseline rate of mammary tumors.

In conclusion, we strongly support FDA's previous decisions to deny approval. The risks that we know are reason for concern, but it's the risks that we aren't sure of, due to research decisions, that are the most serious.

In conclusion, we urge you to vote against approval, and I'm happy to answer any questions.

(Applause.)

DR. LEWIS: Thank you. Speaker 23, please.

MR. HAFF: My name is Derek Haff. Sprout paid for my airfare and my hotel since I'm here. My wife, Judith, was on your panel last year. We've been married for 25 years, and for 20 of those 25 years, our sex life could be best

described as that of newlyweds.

Five years ago, this fell off the cliff because she was diagnosed with breast cancer. Through hormone replacement therapy, she's recovered almost 75 percent of that physiologically.

She still has libido problems. And because of these libido problems, to say that this is distressing to her is an understatement. She is probably the happiest, most optimistic, most positive person I've ever known, and as a result of this low libido, she's completely -- I don't recognize her sometimes, which is very, very strange.

I have three granddaughters, all of whom very well could run into the same problem, and it's partly for them that I'm hoping that the FDA approves this. One of the speakers before me mentioned that if momma ain't happy, ain't nobody happy, and I have to completely agree with that.

Women's influence in the world, depending on how they feel, is in many cases much greater than

men. They influence children. They influence people at work. And that statement, to me, is largely the reason why I think the FDA should approve this. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 24, please.

DR. KELLY-JONES: Hello. My name is Alyse Kelly-Jones, and I practice obstetrics and gynecology in Charlotte, North Carolina. And I am on the frontline of treating and evaluating patients with HSDD. And I have no financial interest in the outcome of this meeting.

The first thing my patient said to me as I walked into the exam room was, "I feel like I'm dead inside." She was broken. She was suffering. And every time she looked at her husband she only saw a blank face, not the loving, desirable man that she married.

Her lack of desire hurt her husband and affected her entire family. While telling me about her concerns, she paused and said, "There's something broken inside of me, and I can't fix it,"

and she began to cry.

This was not her first visit to me. We had talked about her relationship. We had done a lot of things to help invoke sexual pleasure in her life, but none of them were really working well. She had given her all to treat her lack of desire, but these treatments were falling short because they only address one portion of the element of hypoactive sexual desire disorder.

It's real. I see it in my patients every single day in my primary care practice. I can reliably diagnose it in these patients, and science supports my diagnosis.

Successful treatment of HSDD involves more than just talking to these women. It requires more than just lifestyle. It requires more than just these women being told to loosen up. And yet, it's all too often that is all that is offered to women, and they go online and choose products that are potentially unworthy of their money and unsafe.

They need a medication to help them get control over their lives. They need a medication

that has been found to be safe and effective in over 11,000 women studied.

We know that medicine exists, but whether we can give them the help or not they so desperately need is up to you. Please, ladies and gentlemen, every day my heart breaks when I have to tell my patients, women I have come to care for after years of seeing each other, that I have little to offer. In fact, today I have been moved to tears multiple times by these patients' stories.

When next a patient walks into my room and tells me she feels dead inside, please help me tell them, we can bring back your enjoyable life. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 25, please.

DR. WHELIHAN: Hello. I'm Dr. Maureen Whelihan from West Palm Beach, Florida. I'm an OBGYN, and I have no financial interest in the outcome of today's meeting. I am the ACOG District 12 advisory board member. I'm the past president of the Florida OB/GYN Society. I am the

past president of the Palm Beach County Medical Society.

I have advocated for women throughout my entire career, which is about 18 years, and I've been practicing sexual medicine for 10 of those. But today I'm here to advocate and speak on behalf of myself and my patients.

I read a New York Times article recently that talked about doctors medicalizing a condition, and I couldn't help but remember how we used to manage depression and anxiety 30, 40 years ago. It was all talk therapy. And while that is effective, it wasn't the answer for everyone.

Then medication started coming down the pipeline, some with difficult side effects, prolonged drowsiness, appetite stimulation, and a host of other drug interactions, but it was the best we had for managing our patients with depression and anxiety.

Over the years we've improved upon the side effects and the interactions and how these drugs are managed. And today the pipeline still flows

with even better management for depression and anxiety, which has helped our patients become fruitful members of society and maintain their relationships with healthy families, no more insane asylums.

The savvy consumer that comes into my office today, they are tough. They have already Googled their condition. They've WedMD'd everything. They know what they have, or at least they think they do, and they're there demanding a treatment.

Now thankfully, patients are quite unique in what they ask for. Some just want me to tell them nutritional and exercise routines, which is fantastic, which is where I like to begin because wellness starts the whole conversation. Some recognize that they just simply want to have talk therapy because talking about it makes them feel sexy, and so that works great for that client.

Yet the third client is saying, I need a medication. I recognize that there's a biological change in my body that happened, and there must be a pill that can help me. And we've each managed

patients who like a mixture of all those things. And I sit there and have a reasonable, evidence-based discussion with my patients day in and day out, and we talk about the risks, benefits, and alternatives of all therapies.

I sit here today and worry about us talking about syncope, and I think, my gosh, I do GYN surgery, and in every consent I say a risk of death. Should I be afraid of what I do in managing patients when in fact I'm asking them to risk death to have surgery with me?

So I ask you today to consider flibanserin moving forward, and give me an option to take care of some of those patients who recognize that need.

(Applause.)

DR. LEWIS: Thank you. Speaker 26, please.

DR. TAPSCOTT: Good afternoon. My name is Ashley Tapscott. I have no financial disclosures for this event. I am a board certified urologist practicing in Charlotte, North Carolina.

I completed a fellowship in male and female sexual dysfunction at the Cleveland Clinic.

Because of this training, I have the unique privilege and ability to treat both sexes, and oftentimes both partners together in my clinical practice.

With regards to my male patients, I have many well-established tools for treatment. I have guidelines. I have approved medications. This allows me to treat these males with conditions causing severe bother and distress, like Peyronie's Disease. In fact, this condition, Peyronie's Disease, or penile curvature, was so bothersome that the FDA, physicians and men were willing to assume serious risk, including penile fracture, to have a choice in treating that disease.

I see men with swollen and bruised penises, penile hematomas, and I discuss penile fracture in my office with my male patients every day. Please trust that I can talk about syncope and fainting. If I can say penile fracture, I can say fainting.

(Laughter.)

DR. TAPSCOTT: For my female patients, I have an empty toolbox. I can only offer off-label

treatments for which they are uncertain and fearful. I must ask them, "What would you do if you were not afraid?" And in turn, they ask me, "What approved treatments do you have?" I want you to hear the options that I tell my patients.

(Silent pause.)

(Applause.)

DR. TAPSCOTT: Silence is golden. Silence is also very uncomfortable. And while it appears that I have nothing to say, the real truth is that I cannot currently add anything of value to treat my patient with HSDD. I am most uncomfortable with this glaring truth.

With flibanserin, the efficacy has been proven. The safety, as you requested, has been demonstrated again and again. We must allow our female patients to have an FDA approved treatment option.

The success story for men began a long time ago with treatments for their sexual dysfunction. Help me turn the page to start a new chapter to complete a successful patient dialogue. It is

time. Time to end the silence, to change history to herstory. Let's do it together. Let's do it today.

(Applause.)

DR. LEWIS: Thank you. Speaker 28, please. Is speaker 28 here? There she is.

MS. PALIM: Hello. My name is Erica Palim, and I have no financial affiliation with the pharmaceutical industry. And I hate public speaking, but I'm here anyway.

I've been happily married for 25 years. I have four wonderful children, and I practice securities law in Washington, DC. I am here today because I want to help other women who are suffering from HSDD.

I am here today to tell you, HSDD is not a figment of a woman's imagination. It's not a fiction invented by the drug companies. And it's not a disease forced upon women by the medical community. HSDD is real. I know because I had it.

When I was 24 years old, I was diagnosed with breast cancer, and when I was 36, I had a

prophylactic oophorectomy after I discovered I carry the genetic mutation knows as VRCA1. When my doctors advised me to have my ovaries removed, I was clearly informed of many of the potential negative consequences of surgical menopause, but no one ever advised me that I was at an increased risk for HSDD.

However, within a couple of weeks of my surgery, I no longer experienced any of the enjoyable physical sensations that have always accompanied sex with my husband. No warm feeling inside. No heightened sensitivity to touch. And definitely no orgasm. Nothing. It was like a car battery that was dead. I kept turning the key, but no matter how hard I tried, the engine just wouldn't come on.

I think an active sex life is an important, healthy, and natural part of a loving relationship. Not only was I extremely upset and saddened by this complete and sudden inability to experience any of the physical pleasure that my husband and I had always shared, I was also frightened because I had

no idea what was happening to me or why it was happening. I was eventually diagnosed with HSDD, and within weeks of starting treatment, my sex life returned to normal.

I am here today because I think that our society, our government, and our medical community can do better for women suffering from HSDD. We need to acknowledge that HSDD exists. We need to inform women about its symptoms, and we need to allow women, in consultation with their doctors, to choose a treatment option that is best for them.

I cannot understand a society that encourages sex to be depicted everywhere in not always a positive way, but doesn't seek to encourage sex as part of a loving and healthy relationship. There are so many inappropriate places in our society where sexual references abound, yet the one place where sex should be discussed openly and honestly, in a medical office between a woman and her doctor, it is often not even mentioned.

I do not understand those who do not give

women the respect they deserve by refusing to listen to their very real symptoms, but instead deny the existence of a proven medical condition.

I think it is time to leave behind the outdated, insulting perception of women as immature and incapable of responsibly managing their own sexual health, and acknowledge that a healthy sex life is an important part of any person's overall wellbeing, men and women alike. Thank you for giving me to the opportunity to speak today.

(Applause.)

DR. LEWIS: Thank you. Speaker 29, please.

DR. ADAMS BIRT: Good afternoon. My name is Julianne Adams Birt. I am a practicing OBGYN out of Atlanta. I have nothing to disclose today.

On my last day, a few years ago in a group practice, one of my dearest patients came running up to me. She was sobbing. She was sobbing. She embraces me and she says, "Dr. Birt, where are you going? What am I going to do now? Who's going to fix me?" And I looked back at her and I said, "Dear, you've been a patient of mine for five

years, and I haven't helped you yet."

She kept coming back with her low sexual desire. I thought she just liked me as a person, but I really had nothing to offer. And she looks at me and she says, "Oh, I know. But at least you listen."

So today I wanted to talk to you about what I've been doing for the last 10 years, and that has been listening. I've been listening to countless women who have experienced healthy, longstanding relationships. I'm listening to women tell me that they want to want sexual relationships with their partners again.

I'm listening to women confused as to why they are the way they are. I'm listening to women who stress, they stress over the fact that their marriages or their relationships, as we heard from some other persons today, they may be ending soon. They don't have a way to engage in intercourse again.

I'm listening to women who have tried some other treatment options, and I have learned to use

those options in just my 10 years of being out of residency. And trust when I tell you, medical schools all over this country do not teach us how to look at women, and ask the questions, and find out if they're experiencing female sexual dysfunction.

I'm listening to women who say time and time again, of all ages, they look at me and they say, "If they can fix men, when is it going to be my turn?"

I want to go back tonight to Atlanta, and I want to be able to tomorrow, in my full schedule since I had to take off to come here -- I want to be able to tell them that there are other people who have listened to them as well.

I want them to understand that there are others who understand that their condition of hypoactive sexual desire disorder is real. I want to tell them that HSDD occurs not because they're getting older or they're losing some of their ovarian function, or even their mojo.

I want to tell them that soon, because of

today, there is potential help out there. I want to tell them that there is a drug available that can help them achieve what they are desperately seeking, more satisfying sex with greater desire and less distress.

So next time that patient comes to see me, I want to be able to do more than just listen. And if you help me help her, help them all, what a better place, better time, a better enjoyment that these patients will be able to experience. The opportunity today is for you to say loudly, 1 in 10 women do matter. HSDD is real. Their sexual health is as important as their total global health, and that a viable option is on the way. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 30, please.

MS. HICKS: Hello. I'm Karen Hicks, and I have no financial gain from this experience, and I offer my thoughts from the aspect of safety. My lived experience, in fact, as one of the millions of women who used the Dalkon Shield promoted in the

1970s as a safe and effective birth control. Neither was true.

At the age of 35, like other women here, I had a total hysterectomy and lost not only my fertility, but my healthy experience of sexual pleasure. I feel the pain of the women in this room who I can identify with from a great deal of lived angst like they also have had.

The Shield, however, is a textbook case of flawed clinical trial design. Other notorious drugs join the Shield that exposed millions of women to serious harm, including thalidomide, DES, and the early birth control pill, and breast implants. All of those things were promoted to enhance health and wellbeing and lifestyle, not to treat deadly diseases.

So I, too, have the unmet need and want a safe and effective treatment for my sexual problems. I pursued a doctorate in human sexuality and founded a kitchen table organization advocacy group to demand justice for Dalkon Shield women over a four-year period. And for the last

30 years, I've taught mostly young college women from a feminist perspective on their sexual anatomy and the capacities that they have and can learn for creating healthy sexual fulfillment.

But on the question involving flibanserin, I have several issues. There were more than 10 health conditions that eliminated or excluded women from the clinical trials, and I wonder why? Why were women with depression eliminated?

Well you saw the list earlier today. Why were all those people eliminated from the trials? And women on flibanserin experience serious adverse effects compared to those who are on placebo. And today, I've heard measures of minimizing those effects, those potential serious effects.

Many women withdrew from the trial altogether compared to placebo. What does that mean? Why did they withdraw? These same things happened in the Dalkon Shield case. They dropped out and were never accounted for after that. This idea needs much more serious deliberation. Sins of omission similar to the Dalkon Shield case can have

catastrophic outcomes.

I believe that every woman and every practicing physician in the room today is the most well-meaning, honestly passionate contributor towards wanting to find this kind of a medical solution as I do. But they're all women who were basically in long-term relationships with sad medical conditions, like my own, who have sex at bedtime. And what about all the women in new relationships, or occasional relationships, or want to have sex in the morning or an afternoon delight, or something like that, and don't read patient package inserts?

The current evidence-based research imperative is a huge advance in our finding effective and safe treatments. And the two previous reviews, as Sidney Wolfe described, also failed. In terms of grassroots activism, there's this movement even the score --

DR. LEWIS: Excuse me. Your time --

MS. HICKS: Yes, others also went over their time.

They work tirelessly -- people with AIDS and people with breast cancer work tirelessly from a very grassroots perspective.

High quality evidence-based medicine must not be sacrificed. Movements for social justice must not be tarnished by a deep-pocketed pharmaceutical marketing campaign. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 31, please.

DR. TIEFER: Hi. So my name is Leonore Tiefer, and I paid my own way from New York with the money I earned from 40 years of helping women and couples with serious sexual problems as a clinical psychologist.

We're here today to consider whether chronic intake of flibanserin is likely to help women with real sexual problems more than, say, sex education or counseling. Of course no comparison study was done, and a notably small number of study subjects have ever had the experience of sex therapy or sex education. No wonder there was such a big placebo response. But the important issues today are the

substantial dangers of flibanserin and its limited benefits.

But there is an elephant in the room. Sprout's lobbying effort called Even the Score, that for the last year and a half has publicly accused the FDA of sexism in an attempt to buttress its flibanserin application. Even the Score has used website, Facebook page, paid for congressional briefings and lunches for women's groups, and contrived medical conference exhibits galore, all to allege that the FDA is not taking women's sexual health seriously, and to avoid any mention of the real problems with this drug.

Even the Score solicited angry letters from women's groups and Congress from January 2014 to March 2015, and all of this hoopla has been focused on misinformation. Even the Score's false but relentless incantation that the FDA has approved 26 drugs for men's sexual dysfunction, zero for women, we could recite it in our sleep. But Even the Score's own list shows the lie. Dr. Joffe already explained this. I won't go over it. None of these

are brain drugs. None of them are for chronic use. Most are testosterone. They've not been approved for sexual dysfunction. Twenty-six to zero is a red herring.

Sprout has used deception to mobilize women with real sexual concerns to lobby for their questionable product. They've tried to distract the public, bully the FDA, and they have hampered real sex research.

Fortunately, the FDA will make its decision based on the science, nothing but the science. But make no mistake, Even the Score reveals the methods and values of Sprout Pharmaceuticals. Reject this drug once and for all, and let's move on to really help women.

(Applause.)

DR. LEWIS: Thank you. Speaker 32, please.

MS. ERICKSON: Good afternoon. My name is Jan Erickson, and I'm government relations director for the National Organization for Women. NOW is the largest grassroots feminist activist organization in the U.S. with hundreds of chapters

in every state and the District of Columbia. NOW has no financial disclosure. And to be clear, NOW does not endorse flibanserin or any other drug aimed at helping women with HSDD.

The World Health Organization has adopted a working definition about a fundamental human right to sexual health that recognizes the need for gender equality, and the need for recognition of the value of sexual pleasure enjoyed throughout life in safe and responsible manners. NOW's intention in advocating for an effective treatment for HSDD falls in line with our mission in advocating for women's equality.

With several dozen treatments for men's sexual dysfunction, the first available 20 years ago, it is way beyond time when safe and effective treatments should have been made available for women.

Unless this first safe and effective drug is allowed to go forward, we fear it is unlikely that sponsors of other women sexual desire disorder drugs will want to commit the substantial funds

necessary to get their drug to market.

HSDD is a real health condition with some 43 percent of women reporting having some type of sexual dysfunction, most commonly low sexual desire. It has been recognized by medical professionals for 30 years.

Flibanserin has been tested in 11,000 women, far more than most other clinical trial subject numbers. Those women receiving flibanserin found their HSDD had improved more so than those receiving only the placebo in the VIOLET, DAISY, and BEGONIA trials. As reported, flibanserin showed a statistically significant difference over placebo on three key endpoints, including an increase in sexual desire.

Side effects as reported by a small group of subjects were comparatively mild. The FDA required follow-up safety trial found that women treated with up to 200 milligrams of flibanserin at bedtime had no next day impairment of driving ability. This is a safe drug.

Most compelling are the brain imaging

studies, which provide graphic evidence that women suffering from HSDD have different pre-frontal brain circuitry brain response to sexual stimuli than women who do not report HSDD. These images attest to what should be obvious; there is variation in the level of women's sexual desire.

Some advocacy organizations that work on women's health issues have suggested that backers of this medication are simply engaging in medicalizing, that is attempting to manufacture a health problem when there is none. The brain imaging studies should disprove that allegation beyond a doubt.

Most importantly, when 10 percent of the surveyed female population report very low or no sexual desire, and we know that many are turning to risky drugs sold over the Internet, it's time to start believing what women say about their sex lives and to provide safe and effective drugs and devices for their use. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 33, please.

MS. CANNER: Hi. My name is Liz Canner, and I have no financial ties to Sprout. I'm here today because I'm very concerned about this application, but I want to start by saying that I have real sympathy for the women who presented today who clearly have a lot of pain from their sexual desire issues. And I do hope that someday something is developed for them that actually works and doesn't have such severe health risks. And I think we have to take that very seriously, those health risks.

I worked for a drug company that was developing a drug to help women with female sexual dysfunction, and I thought they were really onto something and I started filming them. And I ended up documenting the race to develop a female Viagra drug for nine years.

My documentary is called Orgasm Inc. It was a New York Times critic's pick and it was broadcast in 11 countries. And in that documentary, I filmed the first FDA hearing for flibanserin, and the FDA did an excellent job. They protected the public from a drug that does not really work and has

serious health risks. Why are we back here again?

I've never seen anything like the Even the Score campaign, funded in part by Sprout Pharmaceuticals. It's an attempt to hijack feminist language of equity and convince women that the lack of drugs for them is an issue of sexism, when it's not. This technique is called astroturfing. It is a devious way to use non-profits as a cover for a marketing and lobbying campaign.

We've already seen that their claims are inaccurate. They're not 26 sexual dysfunction drugs for men and there are actually 2 available for women. And I wonder how can we trust a company that has already engaged in such techniques to advertise and promote this product and handle it responsibly.

There are also serious concerns that were mentioned today about the possible adverse effects. There's vomiting and fainting and fatigue, which of course are not very sexy. I'm not sure how that's going to increase women's desire. Maybe it's the

fact that they're more sleepy and more susceptible to feeling in the mood, I'm not sure.

But the real serious concerns are the more than double the risk of injury than those on placebo. There was a concussion. Three times more likely to have car accidents. There was the cancer in the mice studies. There was the congenital anomalies in two of the babies, and that raises serious concerns about second generation. Could this be another DES? And I think that really needs to be looked at and studied more. There was also mention of circulatory collapse.

This is not a drug like Viagra. It's not something that actually works very well, and it's not taken only when it's needed. It's something that women will be required to take daily, perhaps for the rest of their lives. Where are the long-term studies? I mean seriously, where are the long-term studies to make sure that this is not another HRT that we're looking at?

When you looked at how many women want to stay the study, more of the women on the placebo

wanted to stay in the study than those that weren't. So why doesn't the sponsor think about marketing the placebo? There's no side effects and they'd probably do a lot better.

DR. LEWIS: Your time is up. Thank you so much.

MS CANNER: Okay, I'm just going to end my last sentence. The biggest win for women today would be for flibanserin not to be approved. This would protect millions of us from being deceived into taking a drug that doesn't work better than a glass of wine or two, and can potentially seriously harm or kill us. Thank you.

(Applause.)

DR. LEWIS: Thank you. Speaker 34?

DR. SIMON: Ladies and gentlemen, I'm Dr. James Simon, a reproductive endocrinologist and clinical professor at the George Washington University here in Washington, DC. And I've had the pleasure of working with many of you, including my colleagues at the FDA, over many years. I have no financial interests in the outcome of today's

meeting.

During the more than 35 years of practice, I've seen countless women with low sexual desire, a small subset of whom have HSDD. I've conducted more than 300 clinical trials, including several on flibanserin. In those trials, I dispensed flibanserin to more women than anyone else in the world.

That firsthand experience documented the side effect profile discussed here today, clearly published in the peer-reviewed literature and similar to many other FDA approved medications, particularly the SSRIs. These side effects were generally transient and largely eliminated by nighttime dosing.

The benefits of flibanserin were clearly apparent once the blind was broken, but this clinical trial experience is difficult to appreciate from a study report or a briefing document.

Overall, the flibanserin study subjects were overjoyed, excited that someone, anyone, was

attempting to address their longstanding, seemingly permanent problem of HSDD, a problem either ignored or treated off-label with all manner of junk. Yes, junk, herbs, nuts, dried berries, uninvestigated, unlicensed supplements, and drugs purchased over the Internet. Many were treated with compounded remedies carrying no FDA warning labels, or with male testosterone products, all too often at male doses.

More worrisome, however, are the women I've seen who were given strong dopaminergic agents intended for hyperprolactinemia, Parkinson's disease, and restless leg syndrome. Some lost their entire life savings obsessively shopping or gambling, all in search of their former sexual selves. And those side effects, by the way, are in the package insert of those drugs. So maybe flibanserin's most common side effects of dizziness, drowsiness, and nausea aren't actually so bad.

Beyond risks and benefits, ladies and gentlemen, I seriously have concerns about the

potential unintended consequences should flibanserin not meet the regulatory approval we seek here today. I personally experienced the FDA --

DR. LEWIS: Thank you.

DR. SIMON: -- failures of both Intrinsa, testosterone, LibiGel, $800 million down the drain. With that message, what is the message you're giving women?

DR. LEWIS: Your time is up. We appreciate your comments.

DR. SIMON: Will you be on the right side of history or not?

(Applause.)

DR. LEWIS: Thank you. Speaker 35, please?

MS. WIESEN: My name is Beverly Wiesen, and Sprouts did pay for me to come here today, but they're not making up for the $10,000 or so that I'll lose by being here, so just to be clear, I would have come anyhow. And it's great to see some of you again that I saw here in October.

I wasn't sure what I was going to say to you

here today. I spent time on the Hill yesterday. I listened to everyone's stories, and I still know how I feel. I've been on a four-year journey to find an answer. I've seen over 30 doctors.

I have boxes of FDA approved prescription medication with all manner of side effects in my drawers at home. Not even sure how to get rid of them because there's not a good way to do that.

But I can tell you that I've experienced every side effect known to mankind, things that are not even on the labeling. And I talked to every one of those 30 doctors as they prescribed every one of those medications for me.

I had the rare but serious side effect from Lyrica where my face swelled and my tongue swelled and I had to go to the emergency room. I had an adverse reaction to Elavil -- it's one of your SSRIs -- that raised my heart rate to 110 beats a minute getting out of bed in the morning, opposite reactions.

All of this has thrown me into early menopause, so now I'm on progesterone, with by the

way the side effect is the same as this drug that we're talking about here today. Take it at night, it might make you dizzy. It might make you sleepy. Oh boy, there goes a whole other class of drugs you can get rid of because women won't need drugs to help them sleep.

Just to clear something else up that's bothered me, every single person who spoke here today, this drug is taken prophylactically. It's taken every single day. It's not to make you feel like having sex at night, it's to restore your desire to have sex period. So it's not about do I want to have sex when I go to bed at night, when I'm dizzy or nauseous. It's about do I want to have sex period.

So I want to ask you gentlemen on the panel, the ones of you who are going to vote today, if your wives were afflicted with this, would you want there to be an answer for her? The only drugs that helped me are the off-label drugs. I've had no side effects to those, thank you very much, but they're the only things that help me.

I want the FDA to tell me if they're going to go back and revisit Lyrica, and Elavil, and everything else that everyone has an adverse effect to, that people die from, the men who have Viagra who die because there's a heart implication.

I really think there's a positive effect that can come from this approval here today, and that is that many more women who are unheard, who don't even know that there's a possibility they can talk about this, will go to their doctors and have a conversation. Maybe they don't even go for well women checkups now because they're so embarrassed or so terrified about talking about this subject, and it will open the door for additional conversations with women to have with their doctors to go for well visits and have the opportunity to have this unmet need that you, the FDA, identified in October. It can be met. There will be many more women who get healthcare.

(Applause.)

DR. LEWIS: Thank you. Speaker 36?

MS. HILL GRAY: Hello. My name is Marta

Hill Gray, and I have no financial interests in today's outcome. I'm here today as a women's advocate, and to represent my colleagues who could not be here today: Karen Giblin, founder and CEO of Red Hot Mamas; Missy Lavender, CEO and executive director of the Women's Health Foundation; and Dr. Barb Depree, founder of MiddlesexMD, and a women's health physician for over 25 years.

This is not just a women's issue. For many years now, we have watched the Viagra and Cialis ads. Men have multiple treatments for sexual dysfunction, and that's now the norm. The message that men have sexual needs to be met in order to have complete lives and happy relationships is not only accepted, but sexual dysfunction and treatment options are now a part of our daily television commercial lineup.

What we hear from practitioners in the trenches caring for women is that their quality of life is directly tied to their sexual relationships. Clearly this cuts both ways. Many women have not caught up with men in claiming their

right to have a fulfilling, satisfying sex life. Much of this is as a result of not having any FDA approved treatment options.

To quote Dr. Barb Depree, "There are women who come to me because while they love their partners, they no longer get the sexual urge. They find it difficult to respond when their partners initiate. And sometimes I do find an underlying cause. I'm able to treat a medical problem and make a referral for counseling, and provide compassion to a woman who acknowledges that a relationship is over.

"But other times there's no apparent reason for a loss of desire. And for those women, it doesn't occur to me to say, nothing is wrong with your sex drive. If nothing were wrong, they wouldn't be in my office asking, sometimes pleading for help.

"There's not a lot in my toolkit to respond to these women. There have been very few silver bullets in my line of work, solutions that work all the time for every woman. I don't expect that.

"I do firmly believe that women, with support from their healthcare providers, can make decisions about what might help them and the tradeoffs that affect their quality of life. Each woman can decide for herself, hopefully from options that are safe, efficacious and approved by the FDA, and not limited by the opinions, however well intentioned, of other women or men."

If it were anatomically impossible for women to have intercourse without desire and arousal, I argue that this room would be packed with women and their partners looking for solutions, packed. We stand together to thank the FDA for their careful consideration of this condition, and proposed treatment option before them.

(Applause.)

DR. LEWIS: Thank you very much. Speaker 37, please.

DR. PARISH: Good afternoon. My name is Dr. Sharon Parish. I'm a professor of medicine in clinical psychiatry and a clinical professor of medicine at the Weill Cornell Medical College in

New York City, and I'm the president of the International Society for the Study of Women's Sexual Health, or ISSWSH. I'm also an academic practicing general internal medicine primary care physician. I have no financial disclosures to report.

Recently, a 28-year-old articulate, young woman came to see me seeking entrance to any phase 3 clinical trial to obtain treatment for her generalized acquired persistent low sexual desire. This caused her great personal distress and inter-personal strain in her three-year marriage. Well informed, she explained that she treated hypothyroidism, was not depressed, she loved her husband, and her low desire was chemical. She wanted drug treatment.

As a primary care physician, I understand how to diagnose and manage her HSDD along with treating thyroid disease, assessing depression, and appraising the contribution of other biopsychosocial factors. I deeply wished that I had effective pharmacotherapy to offer her. It was

her choice.

Today's primary care physicians competently use screening and diagnostic instruments, such as the PHQ-9 and the audit. We use assessment and treatment algorithms and pharmacotherapy for an array of comparable bio-behavioral conditions, such as depression, alcohol use disorders, and chronic pain. We are facile at discussing the benefits and risks of medications.

Clinical practice guidelines for these conditions have been widely disseminated through responsible international and national societies' educational programs. I understand that there may be concern once this drug is approved about widespread use and about clinicians' ability to diagnose and treat only appropriate patients with HSDD.

ISSWSH is the largest international, multidisciplinary, academic scientific organization dedicated to research, clinical practice, and education exclusively for women's sexual disorders.

ISSWSH and other large organizations

dedicated to women's health deliver extensive, live and web-based educational programs for a wide array of clinicians, including primary care physicians, gynecologists, urologists, psychiatrists, psychologists, sex therapists, and nurse practitioners.

In fact, we partner with nurse practitioners for the courses that were mentioned here in this room. We present evidence-based clinical practice guidelines for all of the issues that you've been mentioning here today, and we believe that we can provide a forum for the effective treatment of female sexual disorders. Thank you.

(Applause.)

DR. LEWIS: Thank you. Would speaker 38, which I'll mention is our last speaker, please come forward?

MS. FAUGHT: My name is Brooke Faught, and I'm accompanied by my colleague Vikki Pedigo. We have no financial interests in the outcome of this decision today.

We are both women's health nurse

practitioners with nearly 20 years of combined medical practice, 14 of those years in sexual medicine. I have served as the clinical director of the Women's Institute for Sexual Health in Nashville, Tennessee since its inception 10 years ago. We are a division of the largest urology practice in Tennessee, which is comprised of nearly 50 medical providers.

Ms. Pedigo and I are here on our own accord, with the support of our colleagues within Urology Associates. Despite extenuating circumstances, including the complete shutdown of our medical practice resulting in thousands of dollars of lost revenue, as well as the untimely loss of my father on Monday, we decided that it was still important enough, as our mission, to be here in DC to present in front of you.

We also had the opportunity to visit Capitol Hill yesterday to discuss these issues with our state senators and representatives. We received no outside compensation for our efforts. Our intentions here are completely pure, and to suggest

anything otherwise is completely insulting.

(Applause.)

MS. FAUGHT: We stand here today as the voice for the thousands of patients that we see and treat each year, as well as all U.S. women who deserve the right to gender equality and the unbiased consideration of medical treatments.

Compared to the approval process for PDE5 inhibitors, including the substantial potential for adverse reactions, which I might add far outweigh the potential adverse reactions of flibanserin, the question at hand is whether flibanserin is effective and if the benefits outweigh the risks.

I believe the data presented by the clinical scientists, the true clinical scientists this morning, overwhelmingly demonstrated this. The FDA also acknowledged that the benefits of flibanserin are statistically significant.

As with any medication, there are potential adverse reactions associated with flibanserin. Let me reiterate, that the major safety concerns identified today are comparable to or lesser than

the current FDA approved medications, many of which have much less research data and many study subjects.

U.S. women are watching today's proceedings closely. Many of those are my patients. To see countless patients each day who are literally suffering from HSDD and do not have an FDA approved medication to offer them, when we have a safe and effective treatment option here at our fingertips, is frankly unacceptable.

MS. PEDIGO: HSDD is obviously a profoundly distressing situation for women to be in. I think that we can all applaud the strong women who have stood up here as patients today and shared extremely personal stories, and we thank them for that. Their personal stories have definitely been heard.

Every day in our busy clinical practice, we see these women in this type of distress that you've just gotten a brief glimpse of over and over again. They are desperate for help. They're already seeking help, and they're getting unsafe

options.

We're not asking you to pass something that's unsafe. We're asking you to consider strongly, as you've obviously done, something that we feel the benefit does outweigh those risks.

Full disclosure, I am a slow adopter. You guys don't know me. I'm a cautious person. I would not -- I promise you, I would not have come here if I had not reviewed this data in detail and if I did not believe that this is going to be a huge benefit to the women that I serve.

We're asking you to only give that the due consideration. Thank you for your time and for listening to all of us. Thank you.

(Applause.)

Clarifying Questions (continued)

DR. LEWIS: Thank you. The open public hearing portion of this meeting is now concluded, and we'll no longer take comments from the audience. Before turning to the questions at hand for the committee, there are two committee members who didn't have a chance to ask any questions at

all this morning, and I'm going to ask them now if their questions have been addressed. Dr. Bagiella and Dr. Guess.

DR. LEWIS: -- Bagiella, I'm sorry.

DR. BAGIELLA: My question is really to try to understand the meaning of the effect size that was detected in this trial.

The effect size was called small, and it seems small at 0.3, 0.4. Even if it's statistically significant, as a biostatistician, I would put more weight on the clinical significance of that difference rather than on the p-value.

I'm trying to understand -- and this is a question for pretty much everybody -- how that difference can translate into those scales that we were looking at. So the scales were pretty discrete going from zero to 4 and obviously were not linear. An average change or difference of 0.3 or 0.4 points, I quite don't see how to place that.

For probably, the FDA, I would ask whether or not they consider analyzing the data, looking at for example, the proportion of patients who reached

a point of 3 on the FSFI-D scale that was considered clinically important, just to place these differences in a clinical setting, in a clinical meaningful way.

DR. LEWIS: Part of what your -- you're making a comment. And so we are going to talk about that. But do you have -- to whom would you like to ask a question?

DR. BAGIELLA: Well, I wanted to know whether or not this data had been analyzed according to the scale. So instead of taking the scale and looking at it as it was a continuous measure, or whether or not anybody looked at the proportion of patients or women who fell into each of those categories -- because we're talking about non-linear scale and we're talking about a discrete number of categories.

It's difficult for me to understand whether -- if you go from 1 to 1.3, is the same thing as where you from 3 to 3.3, and I don't think that that is the case.

MS. TORRENTE: We have some data that can

help with that if you like. I know the chairman is under time pressure.

DR. LEWIS: Yes. We have quite a bit of time pressure, and we have to get onto the discussion. In a minute or less, yes?

MS. TORRENTE: Sure. I'll show you just things very quickly, one to Dr. Bagiella's question is to remind you. The 1.2 to 6 scale that you're talking about is these 2 questions combined and then multiplied by a domain factor, so these numbers won't match the numbers that you're thinking of. But this reminds you of how these women are moving in clinical terms because I understand you're saying, what does 0.3 mean?

In clinical terms, this is where these women started. The 2.4 is where the mean population arrived, and the 3.2 is where the responders arrived. In clinical terms, I think this explains it.

We have a cumulative distribution by all the cut points of FSFI desire for 147 that puts the patients into the buckets of where they stood, and

I'll show you that very quickly.

This is for all 3 endpoints for study 147. You see for the FSFI desire in the middle, the different cut points of percent change from placebo, so you get greater than 1.2 negative all the way up to greater than 2.4, which is your really dramatic change. You see flibanserin showing positive effects everything over zero. I hope that answers your question.

DR. LEWIS: Thank you. Dr. Guess, did you still have a question or has it been answered?

DR. GUESS: It's about the formula you selected to analyze the data. By standardizing the data for the outcomes, you make two major assumptions: first, the rate of sexually satisfying events and frequency of desire is constant overtime. That is if the person reports 2 sexually satisfying events in 14 days, your formula, it seems that they have 4 sexually satisfying events in 28 days.

This is somewhat concerning since Dr. Slagle told us that some women, at least some women, felt

like the number of sexually satisfying events was not constant and consistent from week to week.

The second assumption is that there is you assumed that there's a random distribution of women completing 14 versus 28-day diaries and that they're evenly distributed between the groups. Otherwise, standardizing can potentially result in an artificial increase in the number of sexually satisfying events per month if one group, placebo or intervention, were consistently lower, if you had fewer days per month.

So I have two questions. The first is, prior to standardizing, did you evaluate the data to confirm that the number of weekly sexually satisfying events was not significantly different from week to week? And the second is, do you have data showing that the median number of days per month the diaries were completed is not different between the placebo group and the intervention group?

MS. TORRENTE: We can show you those data. I think maybe the fastest way to answer your

question is to show you total SSE counts without the standardization. The total count per month which was a secondary --

DR. GUESS: Per week.

MS. TORRENTE: Per week. I can only show it to you -- I think I can only show it to you per month. Here, it is. So this is SSE count not standardized in any way at the end of the study versus the first 4 weeks of the study. This is the last 4 weeks of the study, just total count, clean, no standardization, actually the counts that happened versus the first 4 weeks of the study. So no standardization has been applied to these data. So you can just see the complete increase.

DR. GUESS: You have to do it weekly to really answer the question.

MS. TORRENTE: I do have more data but I don't think --

DR. GUESS: -- biweekly, there's going to be a change that can artificially inflate your number over time.

MS. TORRENTE: I don't think the chairwoman

is going to allow me. I would beg your ability to let us just clarify what is inaccurate information you've gotten about the mammary tumor data if we can have literally a minute on that. I fear that you're going to deliberate on inaccurate information.

Questions to the Committee and Discussion

DR. LEWIS: We're already over time. Thank you.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before us as well as the public comments. We have three substantial issues to discuss prior to voting. So I'm going to now proceed with the first question and panel discussion. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

The first question you'll see on the screen, please comment on the clinical significance of the observed placebo-corrected treatment effects of

flibanserin on satisfying sexual events, sexual desire, and related distress.

I'll ask Dr. Lincoff to start.

DR. LINCOFF: I think the responder analysis is the most important because one can quibble about what a unit change on average means and whether it's significant or not, but I think what's important is placebo-corrected responder analysis.

In their summary for efficacy, they claimed 40-some percent of patients responded to this drug, and that's not the case. The responder analysis showed the placebo-corrected difference was 10 percent.

All this argument about placebo not being necessarily relevant in a real practice setting doesn't matter. We use placebo to sort out what is the specific effect of the agent being studied. And the agent being studied increased the rate of response by any of those measures by 10 percent. Those patients may benefit but we've got -- this is what we've got to be thinking about.

When we're thinking about efficacy, we're

thinking about 10 percent of patients responding and the rest not, and that's what we have to weigh against the safety.

DR. LEWIS: Thank you. Dr. Brandon?

DR. BRANDON: Thank you. I think the bottom line is the difference between statistical significance and clinical significance. I do want to remind you all that I'm a therapist, a clinical psychologist. I've been in practice for 20 years. And for more than half of that time, my focus has been treating women with low desire.

I was on this panel five years ago, so I'm really happy to be back. I can very confidently say to you that these -- clinically, these differences are extraordinarily meaningful. My patients would jump at the chance to have one other sexual event a month.

So I really want to encourage you all to think not so much in terms of the fact that these statistics may not be as robust as we would like, but clinically, they're quite robust.

DR. LEWIS: Thank you. Dr. Orza?

DR. ORZA: One of the ways that I'm struggling with the data is to think about a woman who comes in with a baseline, and then has the average effect size on all three measures from the drug, and then goes to see the clinician.

The way the data looks, she would, on all 3 measures, still meet all of the criteria for having HSDD. So the drug doesn't really -- in terms of trying to get a handle on the clinician meaningfulness, it doesn't really seem to change her status from someone with HSDD to someone without HSDD. It changes her status a little bit from someone with maybe slightly worse HSDD. It's the meaningfulness of that that I'm struggling to get a handle on.

DR. LEWIS: Thank you. Dr. Alexander?

DR. ALEXANDER: My comment actually isn't that much different. I was going to request to see -- and I think it would be helpful to consider what the post-treatment levels of the various main measures of interest are among the treated population.

We probably don't have time for that now. But I think that's just a different way of looking and making the same point, that virtually all of the efficacy data that we've seen has been of relative or absolute differences in comparisons between the two groups, that is the treatment and placebo group.

I will say I've sat at maybe 10 or 15 of these committees, and I'm not that -- I can't recall that many times when we focused on, really, anything other than whether the right endpoints were selected and whether they were met or not. So it does feel a little bit funny to me, although I don't think it's unreasonable to question the clinical importance of the statistically significant findings. But I'll say at more panels than not, we're simply examining whether or not there's substantial evidence of efficacy as defined by whether the endpoints have been fulfilled or not.

I guess my last point is just probably it doesn't take a rocket scientist to conclude, but

where one stands on this issue depends upon where one sits. And we've already heard people say, Of course, this means a lot and others say, really, it's not of much clinical import.

DR. LEWIS: Thank you. Dr. Sturmer?

DR. STURMER: I really see the value of the responder analysis, and I agree with the placebo-controlled obviously. The one thing that I'm trying to follow up here is has anyone ever asked these women who suffer from this how much they would think would be a meaningful improvement? I mean, I hear you that from your clinical perspective, you say it is meaningful, but what do the women have to say?

DR. LEWIS: Dr. Weinfurt?

DR. WEINFURT: Well, it would seem that that's addressed in the data we have been shown, that the ratings of meaningful change have come from the patients within the study. So I take those data to be informative of what constitutes a meaningful change for the patients.

DR. STURMER: But that's based on a cut

point that is a minimal improvement. If you look at what this means, that's not what's met in the change of the mean from baseline to the end of the study.

The response threshold for the SSE, for example, is 1.25 to 1.7 depending on the study. The effect was between 0.5 to 1.0. They're talking about between minimal and no change, and that doesn't answer the question whether the women themselves would think a minimal improvement is meaningful.

MS. TORRENTE: We do have the data if you'd like to see it.

DR. LEWIS: Meaningful?

MS. TORRENTE: We have the data showing that, for instance, for SSEs, the women who said it was minimally improved or most improved, there's a tremendous overlap in those women as to how many SSEs that was because to an individual woman -- even a decrement in SSEs can correlate to an overall improvement in the condition because her desire is better and her distress is low even if

she's having less sex. I can show you those ranges but maybe that's enough.

DR. LEWIS: I think we saw that. Thank you.

Anyone else? Any other comments on this first question? Yes, I'm sorry. Dr. Gellad?

DR. GELLAD: No, that's okay. I just raised my hand. I think I'll echo Dr. Alexander's point in that -- and maybe this will be a little unhelpful. But I think the clinical significance of the observed placebo-corrected treatment effect in the trials is not necessarily the most relevant issue when we're really talking about a risk versus benefit. But if it's just about in these specific trials, I would agree with Dr. Alexander that they appeared to have met the endpoints; at least the primary endpoints.

DR. LEWIS: Dr. Brandon?

DR. BRANDON: Can I just say this is a quality of life issue; this is a mental health issue. So I want to remind everyone of that. This is much bigger than sex.

DR. LEWIS: Thank you. With that, we'll

move on. Basically, in response to the first question, we have some thoughts that the responder analysis would be the most important thing and that we have to take into account what the high-risk placebo response was, that this is a modest improvement and still leaving many patients with the diagnosis of HSDD. However, on the other hand, even a modest improvement may be helpful, clinically, for someone who has HSDD.

So we'll move onto the second question, which is quite a long question, and I'll ask the committee to weigh in on that.

Please take into account the generalizability of the clinical studies to the population of premenopausal women who would likely use flibanserin if approved and discuss your level of concern with the risks of hypotension and syncope when flibanserin is used alone and when flibanserin is used with alcohol.

Please include a discussion of the following:

a) whether The Alcohol Interaction Study,

conducted mostly in men who are moderate alcohol drinkers, adequately assesses risk in premenopausal women and in those who generally drink less alcohol than moderate drinkers;

b) the feasibility of avoiding alcohol indefinitely while using flibanserin taking into account the prevalence of alcohol use in this country;

c) whether alcohol use should be contraindicated in patients using flibanserin;

d) whether a risk evaluation and mitigation strategy is necessary and would be able to ensure that the benefits outweigh the risks of hypotension and syncope when flibanserin is used alone and with concomitant use of alcohol; and

e) if a REMS is appropriate, comment on whether the applicant's proposed use of REMS consisting of a medication guide and communication plan is sufficient to ensure safe use or whether additional elements such as elements to ensure safety use with pharmacy certification or with pharmacy and provider certification are needed.

Dr. Gellad?

DR. GELLAD: I didn't realize I'd be first. Let me make two points, and maybe I'll come back and make some points. The first is about the generalizability, which I think is the most important issue when it comes to really assessing the safety and effectiveness of this drug.

The bottom line, is this going to be less safe and less effective in the population that's going to take it in real life? I think that's just the reality of life. And if it were only given to those people similar to who was in the trial, then I think the risk/benefit analysis is very different than if you say, that's not going to happen.

I guess that's a general point, which will maybe tell you where I'm thinking in terms of what risk mitigation strategy needs to be, should be.

The other issue I'll touch on is the risk of hypotension and syncope. I do not think it's fair to brush off the concerns of syncope as it's just fainting because I think it's really, really important that no one could seem to answer when

this would happen. It's not just orthostatic. Someone can be laying in bed, someone can be at the wheel, and this syncope can happen without really knowledge.

There were no serious adverse events that we can tell in terms of deaths but there was a concussion. I think as you expand this use, it is really, really significant with a drug with this level of effect that the risk of hypotension and syncope not be ignored. So those would be some general comments.

DR. LEWIS: Dr. Bagiella?

DR. BAGIELLA: Would that be possible to know what was the yields from the screened population, just to get a sense of how generalizable these results are? What percentage of the women that were screened actually made it into these clinical trials? Just to get a sense of what percent, for example, was excluded because they were taking one of the medication in the 5-page medication, or in the 3-page medication, or had any other.

So is this representative -- is it 3 percent of the full population that entered the trial or is it 60 percent of the full population?

MS. TORRENTE: What I can tell you is that the screening population, a lot of people who were screened didn't make it in the trial for other reasons. The original screen was not by physicians so they didn't actually have HSDD.

In terms of interfering with prohibited medications, we had about a 5 to 6 percent -- I don't know if we can that get on the screen or not. But we had about a 5 to 6 percent of folks who didn't make the screening because of that.

The interesting thing that I'll tell you is we dramatically expanded the list of permitted medications in 147, and it didn't have that much of an effect. What we did was look at how many medications women in this age group are typically on almost 50 percent report being on zero to 1 drug, the one typically being a hormonal contraception. So we think this actually is fairly representative of the population.

DR. LEWIS: Dr. Alexander?

DR. ALEXANDER: Can you broadcast the questions again, please? The first and the last two are easy. I mean I think it's clear in my mind that the study that was conducted with 23 out of 25 men is not sufficient and should not be used reliably to reach conclusions about the safety of this product in women.

I'm surprised and disappointed -- although I guess maybe not shocked -- but it is worth underlining what we heard, which is that we don't know how REMS work; we don't know the effectiveness of REMS. We've heard from the sponsor that they're going to rely upon REMS to limit the use of this product to the labeled population. And I think one would be hard-pressed to identify any rigorous data that demonstrates that a REMS can effectively do that. This is with the program that's been in action for 3, or 5, or 7 years.

I think the answer is clear that we don't know the degree to which REMS will be effective. There's very little information in the public

domain about how REMS works despite more than a hundred products being subject to REMS.

I think A, D and E are pretty straightforward in my mind. I think it's going to be tough sledding to try to avoid having this product used among women that drink, given what we've heard that 50 percent of women or so, if I recall, are using alcohol that are in this age population.

I don't recall seeing from the sponsor the proportion of women who were drinking alcohol regularly that were enrolled. I'm sure we could view those data. But I think it's going to be tough to keep the product -- to avoid having alcohol used concomitantly with this product.

Whether or not alcohol should be contraindicated, you know, that's the toughest of all of these. I guess I don't have a strong notion about that right now, though the increased risk of the adverse events associated with it is definitely noteworthy.

DR. LEWIS: Thank you. Dr. Gerhard?

DR. GERHARD: Toby Gerhard. This kind of follows directly with some of the points that Dr. Alexander made. I want to focus mainly on the alcohol interaction. I think it's important to be clear that we really know almost nothing about the actual clinical effects of using this product together with alcohol.

We have some indication that there's clearly a concern from very small studies that don't necessarily relate -- I mean, predominantly conducted in men. That certainly doesn't generalize to the kind of clinical impact of this and this real clinical potential consequences.

We've seen results in the trial population when stratified by baseline drinking, but this baseline yes/no alcohol use doesn't tell us anything on what's done in the trial. It's actually almost surprising that you see that kind of difference because many of those women that didn't drink at baseline might have had alcohol during the study and vice versa.

We really don't know at this point, which

makes it very hard to take that into a quantitative risk/benefit consideration when making any judgment about whether this would justify a contraindication.

Last point, similar to risk maps, I don't think we know very much what the actual effect of putting a contraindication with alcohol versus a warning with alcohol, is of putting that in a label. I'm not sure that we are confident that it would have any more of an effect.

DR. LEWIS: Thank you. Dr. Heiman?

DR. HEIMAN: Our names are similar. Did you mean me? Okay. So just to reiterate, we don't have any data from this trial really on women. We have 2 women and yet even NIH has said sex is a biological variable, meaning that the effect on women, we really don't know, which is so unfortunate in this particular case with a centrally-acting drug with these side effects.

I think making these decisions really will take the input of all of us to try to figure out what makes the most sense in terms of safety.

The other thing, when we think about what we can do to advise how to best inform patients who will want this information is how do you get the word out because when pharmacists give you information, how many of us really read that?

Physicians or other healthcare providers, that, I think, people usually listen to, but that would need to be reiterated, and you're going to have to remember that even when you're somnolent. So it's really trying to figure out the best thing to do here because it is not like recommending cautions or warnings about other drugs that one prescribes. Alcohol is clearly a drug, but it's not a drug one prescribes. And most people who drink, except for people who have real problems drinking and have gone to AA or a similar treatment, they don't really view it as a drug. They view it as something they do.

Getting a message out about that and figuring out what to do, to me, is one of the more important things we'll try to do today.

DR. LEWIS: Thank you. Dr. Hanno?

DR. HANNO: Thank you. This is a very difficult decision here today. I think it's obvious the drug has some marginal benefit. The company's met the FDA endpoints that were agreed to.

I'm really not clear why the FDA allowed them to change the primary endpoint on desire, after it had failed the first two times, to one that they knew they were going to make because they had made it twice. I wasn't concerned about that. But it puts everyone -- it puts us in a very difficult position here in terms of how to interpret everything, given that the company has done what they were asked to do.

I think the syncope is really a potential problem, and we have no data on women drinking alcohol. We all know that there's a tremendous difference between men and women in terms of alcohol metabolism, and we don't know whether that's going to change anything, but there's an absence of data.

The other thing I worry about is that

another big population for this drug is going to be postmenopausal women, and I don't know how much safety data we have on postmenopausal women. I was going to ask that earlier. But I think that's critical because we know that it's going to be used in postmenopausal regardless of the label.

Those are the issues. And at this point, in terms of alcohol, not being an expert on this type of issue, I would think until you had data, you would at least want a black box and say you can't take alcohol if you're taking this medication.

MS. TORRENTE: [Inaudible - off mic]

DR. LEWIS: Is it one quick slide?

MS. TORRENTE: Three quick slides. I have but one quick slide of just the safety data without the demographics.

DR. LEWIS: One slide?

MS. TORRENTE: [Inaudible] that the demographics --

DR. LEWIS: Just safety.

MS. TORRENTE: -- they're older and have been in the studies longer and in the relationships

longer.

You can see the common adverse events in postmenopausal women in our one completed study. The event rates are actually lower across events than they are in the premenopausal population. I'll point you to dizziness, somnolence, nausea, all tracking a little bit lower.

DR. LEWIS: Thank you. Dr. Leggio?

DR. LEGGIO: Thank you. I'd like to clarify something first. Some people were using the word "intoxication" for example. And I think it will be important to tease out when we talk about intoxication, which is more typical to be seen in patients without alcohol use disorder versus social drinkers, which is actually the most of the U.S. population, which is in part of the question that the FDA is asking here.

So if a primary care physician has a patient with alcohol use disorder, I think it's out of the question that you should try to avoid to prescribe drugs like this medication with CNS effects. But this is not something that will penalize this drug

because for that type of patient, actually the problem is not about should I or shouldn't I prescribe this type of drug. It's not to address the addiction problem. So it's a different actually domain in the primary care.

I think here, what we are trying to figure out is if the drug is prescribed and the patient will ask the doctor can I still drink my glass of wine at dinner, if the doctor should say yes or not. Then that's the majority of the U.S. population, and most of these women will ask this question to the doctor.

In a way, it's kind of a pity, but I think that's the part we miss in the alcohol-drug interaction. For the two reasons, which are part of the question number A, number 1, the study was done in primarily men instead of women. And number 2, because the type of people that were enrolled in the study did not reflect the light/moderate drinkers that will be the primary people that will receive potentially the prescription.

In conclusion, my point is that the alcohol-drug interaction study really doesn't allow us to provide the data in terms of the safety of the drug in the population that is going to receive the drug, women, in particular, the majority of the population of the social drinkers.

DR. LEWIS: Thank you. Dr. Silbergleit?

DR. SILBERGLEIT: Silbergleit. I just wonder if other people on the panel can help me with precedent here because we've got a lot of drugs that we use clinically that don't interact particularly well with alcohol use and have at least somewhat exaggerated adverse effects with alcohol use.

In most of the cases, I don't have good quantitative data to tell you exactly how many drinks will lead to exactly how many additional side effects, and I don't usually demand it.

Is that something that would be typically demanded of the drug at this stage of review? Otherwise, it seems like -- I mean, we're not seeing life-threatening complications in any of

these trials from this interaction so far. Is there precedent for demanding this information at this point?

DR. LEWIS: Would somebody from FDA like to comment?

DR. JOFFE: This is Hylton Joffe. In this case, there was a signal in phase 3 that prompted FDA to ask the company to do a dedicated alcohol interaction study. A lot of drugs out there don't have a dedicated alcohol interaction study. The problem is we've got this data now, and the question is, what do you do with those data?

DR. NGUYEN: Hi. This is Christine Nguyen. I just want to add to Dr. Joffe's comments. You've seen a lot of comparative discussions regarding safety and why we handle the same safety signal differently. That's done on purpose because the safety signal is not handled in isolation. It is completely dependent on the entire context of use.

As far as the alcohol interaction here, it's a little different in this drug. I mean, we're talking about syncope and hypotension. We're not

talking about just CNS depression when you're giving this drug with alcohol. That's expected. And so I think the signal here with alcohol is a little different.

Another thing I wanted to say is the alcohol study is done in healthy young men. You're seeing the syncope in a population that shouldn't be experiencing these adverse reactions, so we can't really ignore those data.

DR. LEWIS: Thank you. Dr. Gellad, you had another question?

DR. GELLAD: I was just going to be more specific now, specifically around the question of alcohol. I think, unfortunately, for the reasons that were just mentioned, it's really impossible to answer the question about C. I think I'll have to say it is a huge disappointment that in a drug like this, in a situation like this, that there's only two women in the study. It's actually very, very hard to believe that.

So in terms of a REMS, I'm going to be specific, I do think a REMS would be necessary if

you go forward for the specific issue that there are safety concerns, and there is very modest benefit in an average treatment effect in the population specifically being studied.

Again, so if you would expand the population being treated, you're going to end up with a lot more potential for adverse events. And I think that it is clear from the public discussion, from the written comments among the public that there are many individuals who do not technically fit the criteria, as far as I understand, for HSDD who desire the drug. That's the reason I asked the question earlier about samples. There are many, many, many, many people who are going to ask for this drug who have nothing similar at all with individuals in the trials. So I think a REMS is necessary, and a strict one.

DR. LEWIS: Thank you. Dr. Orza?

DR. ORZA: Just following up on some of the comments that were made during the public comment period. With respect to B, I think if we did have the answer about alcohol -- and I agree with the

others; I wish we had it -- that there's no reason to think that this population of patients and clinicians would behave any differently with respect to whatever guidance we give them than any other group of patients.

It's not that alcohol and the guidance we give about alcohol in the label or the REMS or whatever should be appreciably any different for this drug and this group than any other group.

DR. LEWIS: Thank you. Dr. Sturmer?

DR. STURMER: Maybe I'm completely wrong here, but bear with me. Given that we have some concerns about who is eventually going to use the drug and that we essentially have no information, no good information at least, on the incidence of potentially severe side effects, has anyone ever considered the postmarketing study requirement before we think about REMS? Shouldn't we know what we are talking about?

DR. LEWIS: Thank you. Dr. Lincoff?

DR. LINCOFF: I agree that the alcohol study should've been done in women, but I think we can

still gain something from it because if heavy men have the effects, which they did, then I think we can assume lighter-weight women will as well.

I think we ought to take the worst case scenario and say this is where the choice comes in that many of the speakers talked about, the public speakers. It works in 10 percent of women. If those women have a response, then I believe that the alcohol should be contraindicated or clearly documented that that's a problem, and that's a choice people could make, just as there are other drugs that interact adversely with alcohol that people choose to take and they choose to abstain from alcohol. And if they don't, they recognize the risks. I think this is a situation where a woman who is responding to this can make the decision that she will abstain from alcohol.

I don't think we ought to be preventing the drug from being available to the group in whom it was studied because of the concerns about who it will be applied to who weren't studied. This is always the case. I think most of our efforts on

risk management should be aimed at making it clear that the risks are unknown in all those other patients that weren't studied in the trial.

The trial inclusion criteria were appropriate. They were trying to focus on the group that actually had the disease under evaluation, and they shouldn't be penalized for not having a broader group that wasn't the target population. And we ought to focus our risk management on making it clear that it's potentially dangerous in higher risk patients who weren't studied in the trials.

DR. LEWIS: Thank you. Dr. Bagiella?

DR. BAGIELLA: It was already answered.

DR. LEWIS: Dr. Gerhard?

DR. GERHARD: Another point that's kind of echoing something that was said by Dr. Sturmer, I think the idea may be that we could consider -- and that's, in a sense, a question to FDA -- whether there are mechanisms for this, whether there are ways to restrict access to a population that we have at least some reason to

believe that we see some effectiveness, and use that population to gain more information about the effectiveness, but also safety outcomes in real-world use.

So have strong requirements for postmarketing safety studies, and there would have to be discussions of what these requirements exactly are. I think a combination of the two might put us in a position that we can allow a drug entering the market without putting too much risk or putting the overall population at too much risk of the drug that we clearly have a lot of open questions about in terms of the safety profile.

DR. LEWIS: Thank you. Dr. Alexander?

DR. ALEXANDER: I just want to respond to your comments, Dr. Lincoff. I guess I'm not comfortable assuming that the effect of alcohol in women is just going to be the same as it is in men. And if it's worse, that is a greater potentiation of the adverse effects of the product. We don't know how much worse.

So I don't think it's fair to just -- I

mean, I can appreciate taking the evidence that we have and saying, well, assuming that it's the same in women, then I personally am comfortable with the risk/benefit balance. But I'm not comfortable with that assumption, nor am I comfortable saying, well, it's the same but could be worse but we don't how much; but women are more sensitive to alcohol than men. The answer is it was only 25 people. I think it needs to be studied in women.

The other thing I'll say is I think you're right that the agency makes it very clear that they don't regulate clinical prescribing; they regulate drug approval and drug marketing. With that said, the agency does have an obligation to oversee and ensure that the safe use of products, broadly speaking -- and there's plenty of precedent for the agency taking regulatory action, including requiring market withdrawal for products that aren't used according to the intended label.

I'm also I guess making the point that I don't think it's fair to say that the agency's job is to say, well, the risk/benefit balance is

favorable in the approved population, and how it's used in the real world, well, that's up to clinicians and patients and other stakeholders.

DR. LEWIS: Thank you. Dr. Leggio?

DR. LEGGIO: Yes. I agree with Dr. Alexander. I think if we had the worst case scenario, we will not have maybe this discussion. But the lack of women pretty much in the alcohol interaction study and the drinking criteria used for inclusion really did not allow us to say that what we see in the alcohol-drug interaction study is the worst case scenario. So it's at least possible to think that social drinker women will have even worse side effects.

On top of that, my concern, which kind of echo what one of the FDA members said before, is that we don't see just a sedation, which will be quite expected, in a way less worrisome, but we see this cardiovascular, this potentiation of cardiovascular effects, which is not something typically seen in the drug-alcohol interaction studies.

MS. TORRENTE: Madam Chairman, I do have one slide that might help clarify --

DR. LEWIS: I don't think anybody has a question for you. Thank you.

MS. TORRENTE: We did study women, I just wanted to --

DR. LEWIS: Thank you.

MS. TORRENTE: Okay.

DR. LEWIS: Dr. Besco?

DR. BESCO: I just wanted to comment on the risk evaluation REMS program strategies. I think the problem that we see with REMS program is that they're largely voluntary. So we have no assurance that any of these elements that have been promoted are being completed.

I think that for this program, it would be wise to develop an informed consent process where the risks have been documented as being reviewed with the patient. I would also like to see as a pharmacist potentially having a carbon copy of that consent to know, as my own personal assurance, that the patient has been properly educated on the

components.

I also think there are some good REMS programs out there that are very robust and have a very good post-approval mitigation plan in existence. Recently, Lemtrada, we are required to conduct three 6-post-month evaluations about side effects, and labs, et cetera, and meaningful things about that therapy. So perhaps we need to think a little bit broader with this drug, thinking about the generalized use that we would predictably see with it.

DR. LEWIS: Thank you. Dr. Silbergleit?

DR. SILBERGLEIT: I think the question with the REMS is going to be an important part of this, but I think that's mostly question 3, right? The general REMS approach? Right now, we were just talking about the alcohol, right?

DR. LEWIS: You can weigh in on REMS for 3, yes.

DR. SILBERGLEIT: I think there's going to be a big part of that.

With regard to the alcohol though, the point

I think I'm looking at, social drinkers were included in these thousands of people who were in the trial, right? So I mean, it's not like we're just basing the alcohol interaction based on just the drinking study. There was social drinking prevalent in the efficacy studies, and so that safety profile incorporates that, right? So I think that's an important point. We're not just talking about the alcohol study.

DR. LEWIS: Thank you. Is there anybody from the committee who has not had an opportunity to weigh in on this question that would like to comment now? I'm sorry. Dr. Guess?

DR. GUESS: Just the comment about syncope also being exacerbated by CYP3A4 inhibitors, and there's a small line that says that grapefruit juice is an inhibitor. Are there other over-the-counter foods and beverages that could potentiate hypotension and syncope because that needs to be understood before this goes on the market?

DR. LEE: The grapefruit juice study was part of a second CYP3A4 inhibitor study that was

submitted during the second review cycle following the ketoconazole study. Grapefruit juice is considered a moderate 3A4 inhibitor, but the level of inhibition of 3A4 is dependent on the concentration, the sourcing, similarly to like a wine.

In terms of other products that could inhibit 3A4 other than prescription drugs that could be included, that would be possibly red wine, some elements of red wine and other sources, I think Ginkgo. There are other elements, and we haven't come up with a full list. But the grapefruit juice -- other citrus juices --

DR. GUESS: I just think that's important to know.

DR. LEE: And the level of inhibition is difficult to predict because it's a food item, so the sourcing, the concentration, we won't know until -- we don't determine what the level of inhibition is.

DR. LEWIS: Thank you. Dr. Phillips, you haven't had a chance to comment.

MS. PHILLIPS: Yes. Talking about drug interactions and over-the-counters, another CYP group that was mentioned and not really discussed in detail was the 2C19. And one of the examples there is proton pump inhibitors. And you're talking about over-the-counter use; 40 percent of the population self-diagnose with GERD, and that's a very commonly used drug in this population.

So that's another interacting drug I think of that would not be handled by drug surveillance or drug-drug interactions because it's typically very often self-prescribed.

DR. JOFFE: This is Hylton Joffe. I think there's been a pretty robust discussion on A, B, C and some of D. It's not clear to me there's been much discussion on the E. And the comment that Dr. Silbergleit made, made it sound like there's maybe a misunderstanding in thinking that there would be more discussion on REMS later on.

There is some discussion on that after voting, so there may be value in just exploring a little more the REMS options now and get some

thoughts flowing that might help people with those votes.

DR. LEWIS: Others who want to weigh in on REMS? Yes, Dr. Brandon?

DR. BRANDON: I apologize if people feel that this question has been addressed, but my understanding is that the alcohol-drug interaction that we see here is fairly common with medications already on the market. So I'm confused. It doesn't strike me as an unusual profile, and I'm wondering how we guide patients that are taking these other medications and keep them safe because there obviously is a precedent for this.

DR. LEWIS: Dr. Lincoff?

DR. LINCOFF: Since there had been a response to mine, I'd like to clarify because it relates to this. I think alcohol is contraindicated in people who take this, just as it's contraindicated in people who are taking narcotics. People may choose to violate that contraindication even if they're educated, but that's a choice that people make if informed.

For the people who are going to take this, I think that we should have a strong contraindication, and I think that should be part of the REMS program. I also believe that the REMS needs to focus on the appropriate indication. Although we don't disregard how the drug is going to be used after it's approved, it's also not fair to refuse to approve a drug because it could potentially be applied to the wrong population.

What I meant, and what I continue to believe, is that that's the role of the REMS, is to, at whatever level of intrusiveness necessary, try to assure that this isn't applied to populations of patients that aren't tested and for whom the safety is unknown.

DR. LEHRFELD: I was wondering if I could address the previous question about labeled products with alcohol?

DR. LEWIS: Sure.

DR. LEHRFELD: We did do some pretty extensive label reviews to look through other products, and there are a lot of other products

that have interactions with alcohol. Many of them are CNS depressants that have additional CNS depression because alcohol is a CNS depressant.

So there are a lot of labels that have that type of warning. And we're not talking about a REMS for that actual issue. We're talking about a REMS for hypotension and syncope. And there are not many labels that actually have warnings with alcohol interactions with the drug that causes hypotension and syncope, especially to the extent we've seen. And to go back to the unknowns, we don't really know how women are going to be impacted with this alcohol-flibanserin interaction.

DR. LEWIS: Thank you. Dr. Whitaker?

DR. WHITAKER: Hi. Amy Whitaker. I haven't spoken yet. About the alcohol use, my Gestalt here is to echo Dr. Silbergleit that the main studies did include women with social alcohol use, and we still saw the serious but rare serious side effects.

So a full contraindication, to me, seems going a little too far, and that a strong label or

a strong medication guide, whatever we or you decide for your REMS strategy, would be sufficient as opposed to saying it's completely contraindicated because those women were included in the studies.

In terms of our REMS approach, to address E, which hasn't been addressed very specifically at this point, I do trust patients and their doctors, if they are well-informed, to make informed healthy decisions about what medications are appropriate and what the risks are.

So I would favor very strong REMS in terms of education without necessarily the restrictions that will severely restrict access like the ETASU, with pharmacy certification and provider certification needed, because I think those ETASU elements are pretty restricted, if I'm remembering the definition correctly, when it was discussed earlier, and that they are probably a level that is not needed at this time.

DR. LEWIS: Thank you. Anybody else want to weigh on ETASU? Dr. Besco, first.

DR. BESCO: I think it's important to remember that there are different levels of leverage strategies that we could apply with an ETASU. It doesn't necessarily have to go to the degree of pharmacy certification. It could be that informed consent process that I described earlier.

I think we just need to realize that an effective safety program requires us to leverage strategies to be most effective and to keep patients safe. So we need to not just rely on one method of risk mitigation. We need to think about a collection of methods that when brought together has a high leverage in keeping a patient safe from harm.

DR. LEWIS: Dr. Gellad?

DR. GELLAD: I'll comment specifically on E. I do think additional elements to ensure safe use is needed for the reasons that I've mentioned, the reasons that Dr. Lincoff has mentioned about risks and benefits. I think provider certification, again, will ensure that this is prescribed to the population that needs it and not to the population

that does not.

I think that every patient who has this condition will most likely be able to find a provider who is certified, given that they'll be interacting with primary care or their OBGYNs or their psychiatrists.

DR. LEWIS: Thank you. Dr. Silbergleit?

DR. SILBERGLEIT: Again, I had a question about enforceability of REMS from the agency. I think you mentioned that there were elements that are enforceable and elements that are harder to enforce and whether you make any judgements about the applicant when making that decision.

DR. LEHRFELD: I'll try to take that. If you're referring to my presentation, I was referring to -- when I was referring to things that weren't enforceable, there were certain aspects of the sponsor's or applicant's proposal, such as the, they term it, responsible launch, or that's what they used in their briefing package. I think they used a different term today. And they talked about having prescriber education materials or training

materials.

They didn't include those under the REMS. A REMS is enforceable, and the sponsor is responsible for reporting to the agency through the assessments how they're complying with the REMS. But the components that I talked about that are not enforceable are the ones they're voluntarily going to undertake. And those, since they're voluntary, not under a REMS, we can't review the materials, or see them, or have any say or approve them. We also can't ensure that they are going to continue through the length of time that we would like them to have those elements.

DR. SILBERGLEIT: So as a panel, we should recommend that all those things, if they're going to do them, be included in the REMS?

DR. LEHRFELD: I don't -- the responsible launch -- there are certain aspects that we have not included in the REMS previously, anything related to a responsible launch or not having promotion on television, that's not something we've traditionally included under a REMS.

DR. SILBERGLEIT: Because I do think the greatest risk in this product is going to be in the people who use it as -- the populations that aren't indicated and people who use it the way it's not indicated.

So I think there are certain drugs that we see that people think if a little bit is good, a lot of more is even better, and this might be one of those, and people who still think that this is an acute therapy rather than what the company is clearly indicating that it is.

DR. LEHRFELD: I will say we do -- as someone else mentioned, the FDA doesn't regulate the practice of medicine, and we don't do that through a REMS either. So we're very conscientious that when designing a REMS program, our intention would not be to limit off-label prescribing. It would be to educate about appropriate patient population.

So there are some limitations to that of a REMS, too. We can educate prescribers and have required education as part of a REMS, or educate

pharmacists as required education, or educate patients as required education. But we can't -- we try not to limit the practice of medicine, who they can prescribe it to. We can just educate them.

I also did want to address the point about having a patient-prescriber agreement form. I will say traditionally we have had patient-prescriber agreement forms. They are linked to pharmacy restricted distribution. Because the patient would be signing that agreement form with their prescriber, and in order to control the dispensing of the drug, that happens at a pharmacy level.

So although we could say that the prescriber has to sign the patient-prescriber agreement form, but if you want verification it's been done, usually -- it has always potentially been linked to pharmacy-restricted distribution. So there is burden associated with all of these different elements to ensure safe use.

DR. LEWIS: Thank you. Dr. Phillips?

MS. PHILLIPS: Thank you. Marjorie Shaw Phillips. It was interesting to hear that comment

because I think restricted distribution systems through pharmacies have not been terribly effective, and they've been very burdensome. But I do feel strongly that both prescriber certification to make sure that only those prescribers that really understand that narrow group of patients that might possibly benefit, and then ensuring that there's some documentation that that discussion between the patient and provider is not only done in a thorough manner but that the patient acknowledges all of those points.

Rather than just throwing the "well it's safe and effective" and throwing it out there, I think, is a very dangerous thing to do because the public already has a perception that this is safe and effective. And if the FDA approves, it's going to be used in a lot of patients where it's going to be either effective, more safe. So I think those two elements are really important for ensuring safe use.

DR. LEWIS: Thank you. Ms. Orza?

DR. ORZA: I need an answer to a question

before I can make a comment. Are the SSRIs, do they have a requirement for provider certification? This is going in a direction that's making me uncomfortable, and I'm trying to put my finger on why.

Most of my concerns about the side effects, the safety profile, come from the fact that I feel like on the benefit side, it's what others have called a marginal or an effect that we're having trouble really getting our hands around how meaningful it is.

If we had a really robust, convincing treatment effect, I wouldn't be worried about this side effect profile because it's similar to other drugs. I think we can trust the providers and the women who will be taking this drug to sort it out, at least as well as they can with any other drug.

So it's really the first part of the equation that's giving me the anxiety about the second part of the equation. But it's sort of trending toward like we need to put all these extra controls on this drug, and I think that's what's

giving the public the flavor that we think there's something about women that they need more control than other people do.

DR. LEWIS: We're going to just take two more comments, and then take a break.

Dr. Johnson --

DR. JOHNSON-AGBAKWU: Agbakwu, thank you. I just had a really quick comment to add to Dr. Whitaker's comment a little while ago. As a general gynecologist for several years, another drug, metronidazole, is something we commonly used for pelvic and vaginal infections that has clear serious adverse events when used with alcohol.

I have had no problem counseling patients for well over a decade on, please do not use alcohol when you take metronidazole; I mean as simple as that. And gynecologists across the country are very familiar with this drug.

I'm wondering if there's some precedent in terms of REMS or other certification process that has been in metronidazole. I'm not aware of that. And for one who has prescribed this, knowing that I

have to counsel and educate my patients on the adverse effects when they use alcohol, it's not been a problem clinically in providing that education to my patients and being able to be confident that they're not going to abuse it or misuse it. I've not had any patients come back with adverse effects from alcohol.

I'm just wondering how much is this a serious concern when other drugs have been used with that same contraindication, and it has not been an issue.

DR. LEWIS: Thank you. I think the concern is this is a chronic -- would be chronic use.

DR. JOFFE: Right. This is Hylton Joffe. This is where we're struggling. You're talking about Flagyl, which is used one -- a very short term treatment, whereas, here you're talking about something that someone would take chronically, day in day out, and how to weigh that against the feasibility of avoiding alcohol that whole time. That's where we're struggling.

DR. LEWIS: Dr. Alexander, Dr. Besco, and

then we'll take a break.

DR. ALEXANDER: I just want to -- there was a suggestion that because people that drank were included in the trial, in the pivotal trial, that we have enough information on them. And there was very little information collected about those people. We know next to nothing about how much they drank, when they drank, how that was temporally related to the adverse events that were experienced, and so on and so forth.

I don't think that we know nearly enough from the trials. Just the fact that they were included and they were moderate drinkers or mild drinkers doesn't provide me with much reassurance when we know that what we've heard is 15 to 30 percent of women this age report binge drinking and 50 to 57 percent report that they're current drinkers in the U.S. population.

Notwithstanding my comments about how little we know about REMS, many years into the program, I don't think that a medication guide and a communication plan alone would cut it, in my mind,

that is that they would be sufficient to ensure safe use of this product if it were to be approved.

DR. LEWIS: Thank you. Dr. Besco?

DR. BESCO: Yes. Just one more comment about my intent of developing a standardized education tool. It's mainly to, I guess, prevent human fallibility. What I mean by that is day 1 -- on Tuesday, I could be on top of my game, and I could remember to educate my patient on every single element that they need to be aware of. But the next day, I could be very busy, have a high patient load and, oops, I forgot an element.

So I think by having a standardized education checklist that the patient and provider sign and says, yes, I have received all the required elements that I need to be aware of to ensure that I use this medication safely. So I just wanted to make that clarification.

DR. LEWIS: Thank you. I'm going to attempt to summarize, and hopefully, I'll capture the general Gestalt of what people spoke about. Otherwise, it is in the record and recorded.

So taking into account the generalizability of clinical studies to the population of premenopausal women who would likely use flibanserin if approved, our level of concern with the risks of hypotension and syncope when flibanserin is used alone and when used with alcohol, I think there's a general feeling that the real-life population will be different. There certainly is going to be broader usage over time regardless of what plans are put in place. And we don't really know what the risk profile is going to look like at that point, but that would not necessarily preclude approval of the drug.

Syncope has been discussed as a significant, potentially significant, medical issue, as well as the hypotension, not just necessarily a minor event because it could occur at an unpredictable time point. It isn't necessarily that somebody would be at home or in bed. They might be behind a wheel or whatever when that occurs.

Looking at the Alcohol Interaction Study, I think there was general agreement that it did not

reflect the group of people for whom the drug would be prescribed because the alcohol usage -- I mean the alcohol study was obviously vastly over-weighted with men, only a couple of women, and therefore it did not reflect the population who would be using the drug. So we really can't tell what that study would look like if it were done in women.

The feasibility of avoiding alcohol indefinitely has generated a lot of discussion. It's not clear that it would be necessary because a lot of the people in the study were described as drinkers, but we don't have much data about that really means. There were not interim assessments of how much alcohol people were drinking and what the time frame was like relative to when they may have experienced an adverse event because it wasn't assessed on an ongoing basis.

Therefore, it's also difficult to make a recommendation about whether alcohol should be contraindicated in patients using flibanserin because we really don't necessarily have the data

based on what we've looked at. Some people were more concerned about the risk than others.

The REMS part was addressed in part. The REMS strategy has been used to varying degrees of effectiveness in the past. There was discussion of developing a standardized informed consent process and using provider certification and pharmacy certification that could limit access but could increase the safety profile.

If it's a purely voluntary program, we don't know how effective it's going to be. Little bit of discussion also about just postmarketing surveys, but again, those are pretty voluntary and we don't know how much information they're going to yield.

Hopefully, that summarized -- okay. We have one more question to discuss, and then we need to vote. First, I think we'll take a 10-minute break, returning at 3:40.

(Whereupon, at 3:29 p.m., a recess was taken.)

DR. LEWIS: I'd like to call the meeting back to order. We have a number of people who are

going to have to make flights, and we want to leave time for adequate discussion. Could everyone please take their seats so we can get started again?

Before we turn to our last discussion point, I'd like to give the sponsor five minutes to correct some misinformation that was out there.

MS. TORRENTE: Hello, everyone. There's just a couple of points that we wanted to clarify from the earlier discussion. There's three very quickly.

The first one is you all saw some teratogenicity data. I think in FDA's presentation, there was some questions, I think, from Dr. Orza about what do those data actually say. And we have a toxicologist here that has obviously studied those data very carefully, and I'd like to ask Dr. El-Hage if she could come to the microphone to talk about the repro-tox findings.

DR. EL-HAGE: Good afternoon. I'm Jeri El-Hage. I'm a toxicology consultant paid by

the sponsor, and I have no financial interest in the outcome of this meeting.

(Off the record discussion.)

Could I have slide RM-63, please? So based on the nature of the tumor findings in the female mice, there's a minimal biological plausibility that the mammary tumors were caused by flibanserin treatment and that the mouse tumors are clinically relevant.

There were no increases in mammary tumors in the two-year rat study in males or females or in the two-year mouse study in males. The slight increase in mammary tumor incidents in female mice is not likely due to drug treatment since flibanserin is not genotoxic.

Flibanserin did not induce any mammary gland proliferation, either hyperplasia or adenoma in mice, and these are typical prerequisite lesions, not just precursor legions but prerequisite set legions for carcinoma. In addition, there was no evidence of mammary gland hyperplasia in mice, in rats, or in dogs treated chronically with

flibanserin.

Per the International Agency for Research on Cancer, IARC, and the Environmental Protection Agency Guidelines on interpreting rodent carcinogenicity findings, if you only see increased tumor findings in a single sex of a single species, that finding is not considered predictive of a human cancer risk. And this was the case with the mammary tumors in flibanserin-treated mice. In addition, the tumor incidence were only slightly above historical control range in the study.

MS. TORRENTE: Thank you, Dr. El-Hage. And just for completeness, the sponsor has offered to do a phase 4 epidemiological study following up on long-term exposure.

The second issue that I'd like to clarify for you is there is a question about whether there were any data on a diversion or date rape potential for this drug, and we've also looked at that very carefully.

What I can tell you is the drug does not have an immediate effect, so it's a gradual onset

pharmacodynamic effect. The only data that we have by week is the eDiary Desire data. And here, it is. You can see at day 7, at day 14 still, there's no effect of the drug on desire, and that's consistent with the animal data that we have.

There's no hypersexuality really seen in our clinical trials. It does not cause an immobility or an amnesia effect. So this is really just a sedative effect, no advantage to using this over a Benadryl-type product. Those are the data we have on that question.

The third point of clarification is just that there is one drug we know of that did an alcohol challenge study. It was different from our study, but there was -- I'll put it on the screen here. It's the PDE5 inhibitor, Cialis, which is chronically administered that did do The Alcohol Study like ours.

Obviously, they did theirs in men and are for men, but just to the question of, are there any labels that have considered hypotensive events that occur with concomitant alcohol use? And here, you

see the PDE5s, and the way they handled it in Cialis, was to say, Do not use with substantial amounts of alcohol greater than 5 units. So that's one of the precedents that we carefully considered. And I thank the chairperson for the opportunity.

DR. LEWIS: Thank you.

DR. JOFFE: Dr. Lewis?

DR. LEWIS: Yes?

DR. JOFFE: FDA just wanted to make one clarifying comment on the Cialis-alcohol interaction.

DR. HIRSCH: Yes. I am Mark Hirsch, medical team leader in urology, and I've reviewed the Cialis-alcohol interaction studies. There were two alcohol interaction studies. And at a dose of 0.7 milligrams per kilogram or approximately 6 shots of alcohol, there was interaction with several patients having postural hypotension, orthostatic hypotension, no syncope. At a dose of 0.6 milligrams per kilogram of alcohol, there was no interaction. That's how the current labeling has come to be.

DR. LEWIS: Thank you. Let's turn to our last discussion question before going through the voting process. That question is on the screen, Take into account the generalizability of the clinical studies to the population of premenopausal women who would likely use flibanserin if approved and discuss your level of concern with any other safety finding.

I'm going to throw it open to the committee to discuss. Ms. Aronson?

MS. ARONSON: Thank you. First of all, I'd like to appreciate the sponsor and the FDA for the presentations today, which I have found really helpful to inform, I think, 700 pages of the written material that we've gone through to get to this point.

As a patient who has experienced HSDD and lack of sexual desire at certain points in my life, I know firsthand that it's a complicated, important issue that has many confounding issues, biological, psychological, and social factors.

As been said many times today, women deserve

to be able to make fully informed decisions and have access to safe, effective treatment. And I guess I want to focus on the "fully informed" as far as the safety.

Someone mentioned quality of life, and I'm trying to pull together one increase in an SSE versus potential risk of the hypotension and syncope, and then sort of the burning questions I still have about some of the unknowns.

One of the troublesome aspects, I feel, is the lack of real long-term studies. My question, for instance, pregnancy this morning, pregnancy outcomes, we just don't know how it would affect people on it. There are only a small number on it, greater than 18 months.

I think I've seen a list of 50 CYP3A4s, and just the complication of trying to sift that through and then not enough information about the alcohol abuse, that's been sort of on my mind. And the number of exclusions in the study, I understand that more frequent studies included more, which was good to know.

I hear from the subjects in the trials, the ones that have come today to say how important this is, and I agree. And I hear the ones who have been on it, maybe short-term and done well. And I wish the people who had fainted or had adverse effects were here as well because I would appreciate that balance of hearing that kind of passion of experience.

I want to just end my comment by saying I have a little confusion about the gender bias and sexism, because I feel it's a little patronizing to kind of say, don't worry about the fainting, or we don't have enough information about the alcohol, but no worry, it's okay. That's where I'm sitting on the safety concerns. Thanks.

DR. LEWIS: Thank you. Ms. Orza?

DR. ORZA: Ms. Aronson reminded me that we should also thank all of the incredibly brave people who stood up and shared their very personal -- it's difficult under any circumstances.

(Applause.)

DR. ORZA: I wanted to follow up on the

generalizability question to something that Dr. Lincoff said. It is true that we always imagine that a wider population than the one that was tested will be exposed to this drug, and that the initial indication for which a drug is improved is often just the doorway to get it on the market, and then it's much more widely used.

In this case, it feels like the population that was tested is so very circumscribed and narrowed. And I wonder if we ever get to a point where it's too circumscribed and narrow. I mean, if we think this was a drug for diabetes, or a drug for arthritis, or a drug for hypertension, and the population was so carefully carved out with that 5 pages of exclusions or whatever, would we have confidence that it was, in fact, a good treatment for the population that suffered from diabetes, or hypertension or arthritis?

DR. LEWIS: Thank you. Dr. Curtis?

DR. CURTIS: Yes. I'm still concerned, as has been mentioned, about -- it seems like there are a lot of situations in addition to alcohol that

are going to increase the drug and possibly lead to some adverse effects. We've talked about the CYP3A4 inhibitors; I think hepatic impairment is also mentioned in the drug label.

So again, it seems like we're really narrowing this population who may get marginal benefit and be safe once we exclude all the other people that for whom this drug may be elevated and lead to adverse effects.

I did have one question I guess for the FDA staff. Can you remind us about postmarketing studies and what the enforceability of doing those postmarketing studies is?

DR. NGUYEN: Yes. This is Christine Nguyen. When we require a postmarketing study, it is enforceable, and we do have milestone needs that the sponsor must meet. As in anything else, there may be unexpected events that occur after the drug is marketed.

So yes, it is enforceable. I guess my point is, we don't always get the data that we think we would at the time of approval, but yes, we can

require those studies.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: I want to comment on generalizability, but first, because you brought up postmarketing, I think one of the issues with this drug is that the outcomes of interest are going to very difficult to capture outside of the clinical trial setting unless you have a really robust system of finding those outcomes. So I think that's an important consideration for postmarketing.

The issue of generalizability, this is probably a nonissue, but it hasn't been addressed so I just wanted to ask. I mean HSDD does not exist anymore, technically, so can someone just comment on the new DSM-V? It's probably a nonissue, but I just want to hear it addressed from either the sponsor or the FDA, or the applicant. Sorry.

DR. LEWIS: Go ahead, sponsor.

MS. TORRENTE: Sure. We do have a comparison slide. I would have had one our experts

do it, but in the interest of safety, I'll muddle my way through it.

You see here, the DSM criteria for hypoactive sexual desire disorder, DSM-IV in the middle column, DSM-V on the right, both require deficient or absent sexual fantasies or desire for sexual activity, both require marked distress, both require that the condition not be better accounted for by their medical conditions, medications, or relationship issues. And DSM-V adds that the symptoms had been there for six months.

Of course, you're right; the DSM-V does put arousal disorder in the same bucket sort of criteria. I think what we heard at the October FDA meeting from nearly all the experts was that as to study inclusion and labeling, it would be inappropriate to mix them because of the dilution of one population by the other and the difficulty in seeing a clinically meaningful effect with all that noise in a polluted population of two different indications.

DR. LEWIS: Thank you. Dr. Alexander?

DR. ALEXANDER: I have a moderate level of concern, is the bottom line. It's interesting. You know, the FDA wrote a letter, I guess a complete response letter or something, a CR letter, from 9/2013 where the applicant was recommended to identify and assess the efficacy of the study drug in a premenopausal women population in whom a larger treatment effect size may be demonstrated to maximize the benefit/risk calculation.

That feels kind of odd to me. I mean, I can appreciate it, but it also puts in a pickle of having a less generalizable, externally valid study result at the expense of having made the effort to show a greater efficacy, which it's not clear to me was actually demonstrated.

It's tough to know exactly how poorly generalizable the study population is. It would have been really helpful to see a Venn diagram, for example, that consists of all women of the age and then consecutively, how many are ruled out based on all the various exclusion criteria that were applied.

Similarly, the sponsor in the tables that were provided, at least in what we've seen so far, you know, all the tables about the study population were age, race, and sex. But what about comorbid conditions? What about mental illness? What about dysthymia, and not just depression?

We heard about those around the edges. What about alcohol use? We heard about all of those around the edges. But the bottom line is I think that there's actually data in these 700 pages that one could use to actually much more quantitatively to identify just how poorly generalizable the study findings are, but those numbers aren't at the tip of my fingers.

DR. LEWIS: Thank you. Dr. Bagiella?

DR. BAGIELLA: I have a comment that is very similar to that. The fact is that we didn't have enough information in what we have seen about the generalizability of this population.

It's really very hard to determine whether or not the samples that were included in these trials were really the ones that are going to, if

approved, benefit for taking this drug. So it would have been nice to have more information on that.

DR. LEWIS: Thank you. Dr. Lincoff?

DR. LINCOFF: I'm sort of confused why we're saying that it's difficult to generalize to the populations being studied. This was supposed to study patients with HSDD. And by the definition, the third point, is the sexual dysfunction is not better accounted for by another AXIS-I disorder, except another sexual dysfunction, is not to exclusively to the direct physiologic effects of the substance, drug abuse or medication or general medical condition.

To my mind, the exclusionary criteria here excluded patients that would've fallen under that so that it made the patients meet the criteria of HSDD. That, certainly, I recognize is not going to be the population that it's extrapolated to, unfortunately, when it gets into practice, if it gets into practice. But I don't think that there was anything done wrong in the design of these

trials. It seems these exclusion criteria were necessary to make sure that the patients met the diagnostic criteria for HSDD.

DR. LEWIS: Thank you. FDA would like to make a comment.

DR. CHANG: Yes, Dr. Lewis. We do have a backup slide that would show the comorbid conditions of the study subjects from all the phase 3 trials. It's in Dr. Easley's backup, slide number 10.

DR. EASLEY: You can see the left column is the phase 3 study that had fewer exclusion criteria, so a more generalizable population, still quite healthy. The most common preexisting medical condition was headaches, seasonal allergies.

Could you go to slides 8 and 9, please? These are the prohibited medications, so while it's true that just by virtue of diagnosing someone with HSDD, you're going to be excluding a tremendous number of medical conditions, there are also numerous medications that may be used over there counter, wherefore you're treating a temporary

condition that were excluded, so you're not actually getting the full picture of what someone in the general population is going to experience who may use concomitant medications.

Slide 9, yes, go to slide 9 too; yes, that's a continuation. Study 147 did allow more medications that are shown on this slide, so that was helpful.

DR. LEWIS: Thank you. Dr. Sturmer?

DR. STURMER: Thank you. I just wanted to follow up on the idea that the assessment of the safety outcomes would be difficult in a non-randomized study. I don't understand that. Can you follow up on that?

DR. GELLAD: It's not that it's randomized or non-randomized, but truly capturing true syncope and true hypotension would require -- you couldn't just do a claims database analysis. I mean, you'd have to -- there would be patient-reported outcomes, but you'd really have to think about how to capture these on a large enough scale for events that are going to happen in the home that may not

come to medical attention. That's what I mean.

DR. STURMER: But we would still be mostly interested in those leading to accidents, for example, and you could capture that.

DR. GELLAD: I'm happy to discuss it more. I mean, hypothetically, if I have a patient on this drug and it leads to them falling and having a concussion at home that does not come to medical attention, that's something I'm going to want to know even if it does not lead to an accident that has an ICD-9 code in the emergency room.

That's what I'm really getting at, that there are adverse events from these issues that can happen that are not brought to medical attention.

DR. LEWIS: Thank you. Dr. Guess?

DR. GUESS: I had a couple of questions about the inclusion criteria. You mentioned that they couldn't be on hormonal agonists. Did that include IUDs like Mirena IUDs or Depo-Provera?

Also, as far as the persons who were enrolled with hypertension, were they on any antihypertensive medications or were they just

diet-controlled hypertensives?

DR. EASLEY: IUDs were allowed --

DR. GUESS: Hormonal IUDs?

DR. EASLEY: Yes, they were allowed. In terms of --

DR. GUESS: Depo?

(Off mic conversation.)

DR. EASLEY: Yes, I don't believe that antihypertensive drugs were excluded. Perhaps the company can confirm that.

DR. GUESS: And Depo-Provera?

DR. EASLEY: Depo-Provera was allowed.

DR. GUESS: Okay.

DR. LEWIS: Thank you. Dr. Brandon?

DR. BRANDON: Someone had asked or said that they would have liked to hear back from women who had adverse events. And I do recall, I believe, that the woman who had the most severe syncope went back on the medicine after she recovered; isn't that correct? So it was her choice to go back on the medicine. I just wanted to say that.

Also, with regards to the AEs that would

happen at home that we may not know about, I think that will be difficult for us to tease out from the effect of alcohol. If a woman is going to bed intoxicated, and then maybe she gets up to get some water or something and she trips and falls, how would we know if it was because of the alcohol she drank? Because she's at risk anyway; she's drinking before she goes to bed, I would assume.

DR. LEWIS: Thank you. Dr. Gellad?

DR. GELLAD: Really quick. I'm sorry. Just because I saw the benzos, given the alcohol interaction, is there data about benzodiazepines in these, since they were excluded from the trials, benzodiazepines in the use of this drug?

DR. EASLEY: We do not have any data on that.

DR. LEWIS: I'm going to ask a question. Any illicit drug interaction data?

DR. EASLEY: No, and patients were excluded who had a history of drug abuse. But no, there's no illicit drug data.

DR. LEWIS: Other comments? Okay.

Dr. Orza?

DR. ORZA: Sorry. Just about the safety findings, I just wanted to give FDA a chance to respond to what the company said about the breast tumor findings in the animals, if their explanation is why you didn't highlight that for our discussion.

DR. JOFFE: Unfortunately, our nonclinical experts aren't here today. But the truth is this isn't a signal you'd be able to fully evaluate in a premarketing setting either. The prevalence, how long it takes to develop, having enough cases to see anything, even with Sprout's database, even if you greatly increase that, you still wouldn't be able to answer that question.

If we want to look more at breast cancer, a way to do it would be with some type of postmarketing study and maybe -- I don't know if anyone from our epidemiology group wants to comment about that.

DR. MOENY: David Moeny, deputy director, epidemiology. It's true that it's going to be very

difficult to do a clinical trial to assess the risk of breast cancer. In the postmarketing world, it's also going to run into some substantial issues as well. Especially in the United States healthcare system where we have patients moving in and out of healthcare plans, relatively short follow-up time with patients, these things create a bit of a difficulty tracking patients long enough to assess the outcome for the drug.

It will be challenging there as well, but it's probably our best bet for assessing a cancer risk for a drug once it's approved.

DR. LEWIS: Thank you. Dr. Heiman?

DR. HEIMAN: I was just thinking should there be something in the insert -- this is just a general question -- regarding women who are trying to get pregnant, that this wouldn't be advisable to use this while they're trying to get pregnant.

It's kind of an obvious thing, and the main thing is just since it's centrally-acting and increasing evidence is coming out that centrally-acting drugs, not all of them equally,

impact the fetus at increasingly earlier ages, just to be extra careful about that.

But this drug shouldn't be particularly treated any differently than another centrally-acting until we might know more, but more that we just do whatever, because these women are taking the drug for sex, which is a little different than when you're taking a drug for depression, anxiety.

DR. LEWIS: Okay. Any more comments?

(No response.)

DR. LEWIS: All right. So question 3, taking into account the generalizability of the clinical studies to premenopausal women who would likely use flibanserin if approved, what is our level of concern with other safety findings? The committee was uniformly happy with the input of those patients who chose to share their stories with us and very appreciative, hard to capture some of these events, and largely unknown how generalizable some of these safety concerns would be.

Some of the concerns that were raised include breast cancer, which, of course, is a long-term one where it would not practically be able to get data before approval. Pregnancy, especially for people who are trying to conceive, to be especially mindful to make that known that people shouldn't become pregnant while taking the drugs, the other CYP3A4 inhibitors and alcohol. Overall, most people expressed, I would say, a moderate level of concern.

So with that said, we will now turn to the voting process. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and continue to flash even after you've entered your vote.

Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen.

Dr. Bhatt will read the vote from the screen into the record. Then we'll go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want, and we'll continue that until all questions have been answered or discussed.

So first, we have the overall risk/benefit profile of flibanserin, is that acceptable to support approval for hypoactive sexual desire disorder in premenopausal women? A) Yes, with labeling alone to manage the risks; B) Yes, but only if certain risk management options beyond labeling are implemented; and C) is no.

So are you ready? Okay.

DR. JOFFE: This is Hylton Joffe. I just want to make sure everybody is clear on the question before we vote. If anybody has clarifying questions, now is the time.

DR. ORZA: A technical question. Are we supposed to use the A, B and C on the voting -- or, just the Yes/No?

DR. LEWIS: A, B and C correspond to A equals Yes; B equals yes, but only if; and C equals no. So A and B are both yeses, but one is an unqualified yes or less qualified yes, and B is a more qualified yes.

Does that make sense? Yes? Okay. Dr. Gerhard?

DR. GERHARD: Just a quick clarification to FDA. I assume we can state under B whether we would require postmarketing studies or specific considerations in addition to just the risk minimization activities?

DR. JOFFE: This is Hylton Joffe. Yes, I think you have to think through for studies that you feel are needed, whether those studies can be done preapproval or after approval because that will impact your answer here.

If you think a study is definitely needed preapproval before you could approve, then you'd have to vote C. If, however, you feel we need more data, but that data can come in postmarketing, then your answers will be either A or B.

DR. LEWIS: I should mention that after we vote, we are going to go around and everybody is going to weigh in. Yes, so you'll have the opportunity to say what kind of risk management strategies you'd like.

Okay? Are we ready? Okay, let's go.

(Vote taken.)

(Applause.)

MS. BHATT: The voting results. A is zero; B is 18; C is 6; nonvoting is zero.

DR. LEWIS: Okay. Let's start with Dr. Gordon.

DR. GORDON: I don't get to vote so I didn't get a chance.

DR. LEWIS: So we won't start with you then. I lied. I apologize. Dr. Silbergleit? I apologize. It's hard to see you from here.

DR. SILBERGLEIT: What do I do? Explain my vote if I want?

DR. LEWIS: Yes. What did you --

DR. SILBERGLEIT: So I want to thank the review division. I think that if I'd been on this

panel the previous time, I don't think I would've voted the same way that I voted this time. I think that the review division did an excellent of job requesting the material necessary to make a benefit/risk analysis.

We're always faced with not knowing what safety data we don't have would say, so I do think that post-marketing data, in this case, is going to be important.

I think that a REMS strategy is going to be very important because I think that the most likely risk out of this is going to come from physicians who don't use the drug properly because they're not properly educated. So a REMS strategy that gets physicians the information they need to use it properly is going to be key, potentially especially because I have concerns about the marketing of this drug as well, and the physicians might be in a situation where they have to counter a lot of direct consumer marketing that could lead to misuse of the drug.

I think that a very careful postmarketing

enforcement of marketing strategies as well as REMS will be important toward the safe use. But I think that we finally have sufficient data.

DR. LEWIS: Thank you. Dr. Flynn?

DR. FLYNN: So I also voted B, and my background is in patient-reported outcomes measurement, and I did not have concerns about the measures that were used for the outcomes. I thought that the demonstrated benefit was clinically significant.

I guess in terms of the REMS, in addition to addressing alcohol use, addressing pregnancy would also be something that I would want to make sure was included.

DR. GELLAD: Walid Gellad. I voted B also. Just to say a few things, I think if this were the seventh drug in the class, I think it'd be a very different discussion. It was clear from the material that was submitted and from the brave public comments that there are many women that suffer, and that there are many women for whom the drug will work and there are many women for whom

the drug will not work.

The benefits are modest, and I use that -- maybe less than modest, but I think that puts it in good company with other approved drugs.

(Applause.)

DR. GELLAD: What I understand is those benefits aren't average, and there are going to be some people that really benefit and some will not. So I have serious, serious, serious safety concerns. This is probably clear from my comments.

I think the syncope is really important, even if it's rare, because it can be serious, it's unexpected, and you don't know when it's going to happen. And it's potentially accentuated by other things. I think it is not something to just ignore. The study was done in a select population under controlled conditions like any randomized trial. When you extend it to the real-world, things are going to be worse.

So I do think that a REMS is required. I would suggest that prescriber certification would really be the best thing to ensure that the

patients who need it get it, and it's only given to those who fit the criteria. Those would be my comments.

MS. BHATT: Dr. Lewis?

DR. WEINFURT: Kevin Weinfurt.

MS. BHATT: I apologize.

DR. LEWIS: FDA wants to --

DR. NGUYEN: Before we proceed further, for those who voted B, if you can give us a little more specific details on what you would like to see in the REMS, that would be very helpful.

DR. GELLAD: I don't have a huge familiarity with the specifics, but I think -- I'm comfortable saying this drug can benefit women who are similar to those in the trial who have the diagnosis. I'm very uncomfortable saying that there are samples in the office, and someone comes in like they often do to me and others saying that they're having issues with libido. It's not well-investigated; drugs are ignored, et cetera.

I guess I don't have an answer for you other than to say that I think that everything should be

done to make sure that the drug is only given to those who are as similar as possible in the trial. So if it requires -- and one way you can do that is ensure that only those prescribers who see these patients generally would be the ones prescribing them. Sorry for the terrible answer.

DR. NGUYEN: Actually, let me clarify. We have presented some of the options that FDA could consider or considering: a communication plan, the pharmacy certification, prescriber certification. So perhaps you can rely on some of those options as a starting point. Obviously, if you have other ideas, we would welcome them.

DR. GELLAD: Yes. I don't want to take any more time, just to say I think pharmacy certification will be too burdensome. I think prescriber certification is necessary. I think just general education material will not be enough.

DR. WEINFURT: Hi. Kevin Weinfurt. I voted B, and I'm in agreement with my other B colleagues here and echo the prior recommendation for what ought to go into the REMS.

I think it's also worth pointing out because there's been some confusion, I think, about the type of benefit that was observed. It's clear to me that there was very consistent benefit on measures we understand and accept well in the field for some portion of women. Some portion of women didn't have those things. I think that's impressive. I think that we also are going to be looking forward to postmarketing studies to understand for whom this therapy is most beneficial and what other risks are present.

The other thing I wanted to point out, too, was that there were significant improvements that seem to be conferred by other aspects of attending to the patients in these studies through the study protocol. I think that's a design necessity. It helps us understand the pharmacologic effect, but it's also encouraging to people who are suffering from this to recognize that this could be a part of a broader strategy to confer a larger benefit.

DR. LEWIS: Thank you. Dr. Leggio?

DR. LEGGIO: I voted B as well. As you saw

from my comments, I was concerned in particular about the alcohol-drug interaction study. But on the one hand, I echo what my colleagues said, that I took under serious consideration the fact that it's another first drug -- the seventh drug, let's say, for this disorder, but it's the first drug ever.

So balancing the benefits, even if not very strong on the medical disorder for approval versus the risk, I didn't think that the concern about the alcohol-drug interaction was so serious to lead me to vote for C, so that's why I voted B.

With that in mind, I still have some concern for which my recommendation would be to do as part of the REMS, the REMS with the provider certification, just like Dr. Gellad.

DR. LEWIS: Thank you. Dr. Johnson-Agbakwu?

DR. JOHNSON-AGBAKWU: Agbakwu. Thanks. I also, with my colleagues, voted B, and I feel that HSDD is a very real concern. And the findings from the sponsor, I felt that there was clinical significance in the treatment effects.

I do, however, think that there is definitely a need for long-term safety studies, especially around pregnancy and women who are seeking to become pregnant. I think one way to ensure appropriate patient selection, patient education, and counseling is to require some form of physician certification, whether that involves targeted training and education that's documented, especially in terms of continuing education on its process involving standardized tools, checklists as was mentioned earlier, and a detailed documentation at the informed consent process that is documented in the patient records would be something that would be important to include, as well as ongoing postmarketing surveillance.

DR. LEWIS: Thank you. Dr. Brandon?

DR. BRANDON: I voted B, and I am comfortable actually with the sponsor's risk management suggestions. It's multidimensional. I felt like they addressed the safety issues appropriately and will continue to do so. I just want to be conscious of not implementing

unnecessary restrictions, and thus limiting women's access to this medication. Thank you.

DR. LEWIS: Thank you. Dr. Heiman?

DR. HEIMAN: Yes, I voted B. And on the efficacy side, these are very modest results. On the other hand, modest results can make a lot of difference when you're at a certain point in a clinical problem. Therefore, I'm less concerned about this, so this may at least get something started.

With regard to recommendations, I think that -- so I am trying to balance burden on the entire healthcare system from patients through docs or pharmacists, to what still seems to be needed because it's unknown. So at least for the moment, I would think would be indeed provider certification, not pharmacist certification.

It sounds like informed consent would need to go through the pharmacist. I would therefore back off from that. But I think the checklist idea that someone brought up would be a good substitute and hopefully not too burdensome.

The other thing is postmarket, I'd like to see more attention to the alcohol issue and a real study done looking at both low dose, like normal dose that people drink, as well as higher dose, not just these really forced challenges of alcohol, on women of childbearing age, and also following up longer term on cancer and pregnancy, particularly cancer.

DR. LEWIS: Thank you. Dr. Hanno?

DR. HANNO: Yes. I voted C. I really didn't think that the benefits outweighed the risks. Based on that, that's why I made the vote.

DR. GUESS: I voted C. I think, again, there are modest benefits, but as I said, I think there are a lot of assumptions that went into those benefits. There's also a number of risks, and I think simple things like not knowing what over-the-counter foods, costs, or CYP inhibitors, and things that we have to educated about if we're going to prescribe these medications are very important. So when you're doing that postmarketing or premarketing, understanding those things so that

providers who are prescribing it can have those things at hand, be able to counsel their patients appropriately.

DR. LEWIS: Thank you. FDA would like to make a comment.

DR. MANZO: Yes. I know quite a few have recommended prescriber certification without a pharmacy component because of the potential burden. But I want to make the point that in order for us to be able to achieve prescriber certification, to ensure that occurs, that often involves a pharmacy becoming involved. Otherwise, it still becomes somewhat voluntary unless it's tied to dispensing of the drug.

DR. NGUYEN: I want to actually also add some additional clarification. Pharmacy certification doesn't automatically mean that the pharmacists have to counsel the patient in addition to the prescriber counseling. But yes, if we have prescriber certification, the pharmacist has to verify that the prescriber writing the prescription is indeed certified. So it's kind of one requires

the second step.

DR. JOFFE: Hylton Joffe. Dr. Hanno and Dr. Guess, because you voted C, we'd also be interested in hearing what data you think would be needed to ensure positive benefit/risk. And that's the same question for the other folks who voted C when we get to you.

DR. HANNO: Well, I think the alcohol in women and -- I mean, my big concern was the endpoints. One endpoint apparently didn't really matter how many times you had satisfying sex, and the other endpoint failed on the first two occasions and then was dropped to pick up an endpoint that succeeded in the first two occasions.

So the whole thing was kind of squishy to me, and I just -- and if it was very robust, I would have said, yes, this is worth doing. But given the potential for syncope when people are driving and things, days or weeks after they start the medicine, and that it's a chronic medication, I'm not sure there's a whole lot I would recommend that could be done to convince me that it should be

approved.

DR. GUESS: I would ditto the alcohol and then understanding over-the-counter foods and drugs that might affect that syncope and hypotension.

Also, body weight, there were about 55 percent who were overweight, so do normal-weight people have more syncope or underweight people, and really understanding that so that when we're prescribing, that we're making sure we're keeping it in people who are going to be the safest.

DR. ORZA: Michele Orza. I voted no in some degree of agony. I want to make it clear that I did not for an instant doubt that the suffering of these women is real -- I never doubt anyone's suffering -- nor that they need and deserve treatment. Everyone who is suffering does. But the question I felt we had to answer was whether this is the treatment they need and the treatment they deserve. And my feeling is that they deserve better.

I thought that there was enough noise in the data, and the treatment effect was minimal,

marginal at best. And I do have some concern that moving forward that in considering subsequent medications, that FDA will find that the standard is too low and problematic.

I wanted to echo something that another panelist said about the large placebo effect, which does not represent nothing. It represents all of the other things that were done around the drug. Primarily, I imagine simply recognizing that people are suffering and attending to their needs, and I want to make sure that in however the program moves forward that those components of the treatment are not lost.

I don't have the -- I actually applaud the kinds of endpoints that were looked at here. If you contrast this, for example, with testosterone, the sole endpoint is a blood level of testosterone, and there are no endpoints considered that patients actually care about or that matter to patients. In this case, I think the endpoints that were examined were very meaningful and that further work should be done in exploring those kinds of endpoints and

how best to assess them.

MS. BELL-PERKINS: Elizabeth Bell-Perkins. I voted B. It was difficult. I think that what's considered modest or minimal is very meaningful for people who have this disorder. I do believe that postmarketing studies should be done following -- for safety, pregnancy, and I mean the whole fertility, does it affect fertility, the whole piece of it, not just did the pregnancy result in a live birth.

For safety, for alcohol and what other drugs the patient may be taking chronically, REMS definitely, education, and I hope control over the kind of marketing that's done in all medium: print, TV, Internet, social media, and that it should be rolled out in a very careful way. I would hope that the FDA would have some say over that.

A prescriber certification with the pharmacy certification, I like the idea, but on the consumer level, I don't like the idea. To say that, okay, we're going to approve this, and here's some hoops

and things you have to jump through, and then maybe putting a hoop there that you can't jump through -- I come from a rural area, and every little extra thing that has to be done is much more magnified than in an urban area, regardless of economic level.

Although I like the idea of prescriber certification, I don't know that I'm comfortable with that as far as making it accessible for the patients.

DR. BAGIELLA: Emilia Bagiella. I voted C, no. There were several factors that affected my choice, mainly it was my difficulty to really translate the effect size into something that was meaningful for me from a clinical and clinical trial point of view.

The marginal efficacy over a substantial placebo response was too small, in my opinion, to justify the risk that were observed in this trial. In addition to that, the generalizability of the results was another issue where there was very little evidence that this small effect size would

replicate itself in a more general population.

I also thought that there were too limited data on the long-term effects of this drug. This is a drug that is going to be a chronic administration, and so it's going to be given, I heard, for some women for the rest of their lives. And there is not data whatsoever of what the effects are in the long term and how it would be possible to assess the long term effect in terms of side effects, effect on outcomes and pregnancies, and so on.

I also thought that any REMS would be inadequate at this point given that there is not enough information, and it would be very difficult in a chronic population to ask women to stop drinking for the rest of their lives, to stop taking some drugs that they might need for the rest of their lives, to may not become pregnant because they want to have sex and they can't do the two things together.

I think that it wouldn't be difficult to assess what the side effects are going to be in the

long term. A woman who has a drop in their blood pressure, falls into the tracks, and dies there is not going to be picked up by any REMS, and we will never know why that happened.

DR. ALEXANDER: Caleb Alexander. I voted no, and I just want to say it's possible that this product has an untenable risk/benefit profile. So while I will suggest some additional studies, it is possible that no additional studies are going to suffice according to some people's thresholds.

I'd like to see a dedicated alcohol study in women. I'd really like to see a pragmatic clinical trial, frankly, that better reflects real-world populations, though admittedly, this is a bit at odds with the FDA's recommendations a year or two ago to essentially stack the deck in favor of the product by studying it among a more selected population where efficacy is more likely to be demonstrated.

I have some concerns that people don't appreciate the difficulty of limiting products use to the approved indications and that people may

also be vesting more confidence in the REMS program to do so than has been demonstrated to be the case.

If it was approved tomorrow, I think alcohol should be contraindicated, so I guess I've thought a little further about that since an hour or two ago, that a variety of DDIs should appear prominently on the products label; that is drug-drug interactions.

I don't know about limiting DTCA during the product's early market debut. I mean, I would be in favor of that, but I don't know if there's regulatory precedent for that. And I do think an ETASU should be implemented with restricted circulation if it were to be approved tomorrow.

MS. ARONSON: Diane Aronson. I also voted no and for the reasons that have been stated by those that have voted no, and I won't repeat them. Some of them were comments that I made earlier about my concern about safety issues. And I also have a concern about the length of time it may take to get postmarketing information because sometimes that's a real lengthy process. Where it's just

been short term, I have that concern.

DR. CURTIS: Kate Curtis. I voted B, but somewhat a conflicted and still uncomfortable B. There was minimal effect of unclear clinical significance, and I agree with Dr. Orza's comments that women suffering from HSDD deserve better than this. But the drug did meet the prespecified endpoints, and at least for about 10 percent of women, it seemed to be clinically meaningful. There were rare SAEs in the target population but unknown rates of those in whatever the actual use population will be.

I agree with most of the previous comments that there needs to be strong REMS put into place. I was a little shocked to learn that we don't really know how REMS work and how to make them most effective. So just in general, I think we need to do a little more work on that.

But specifically, I think there do need to be some very strong postmarketing studies, a dedicated alcohol study in women as was mentioned, and some strong actual postmarketing studies on

some of the outcomes, not claims data studies, but some studies where we can actually measure the outcomes and try and better delineate women for whom it will be effective because those are the women, pretty much the only women, where the risk/benefit ratio makes sense.

DR. LEWIS: I voted B, a difficult B. And I have the same concerns as everyone, so it was a difficult B because it's not a terribly effective drug. It's a modestly effective drug, and the safety concerns are significant.

I'll add one thing that hasn't really been brought up yet, and that has to do with the effect of people getting drugs through Internet pharmacies and a REMS kind of plan that would be initiated. I could see it working both beneficially and not beneficially. On the benefit side, it could provide access to, say, the rural patient who lives some distance from a large pharmacy that could have a certified pharmacist who could participate in such a plan. On the risk side, I believe that some patients obtain pharmaceutical products, even those

that are supposed to be restricted to prescription-only use, through the Internet.

So many people have computer access. It could provide the opportunity for educational video, for another way to introduce an informed consent process, especially for people who tend to not read everything carefully that's put before them. That's another option for providing patient education about risks and potential benefits.

DR. WHITAKER: Amy Whitaker. I voted B as well. I think it's exciting that we'll have a drug in the armamentarium for the treatment of HSDD, although I think we all wish that it was a drug that was a better one, but that, overall, the very modest benefits outweigh the real but infrequent risks associated with it as mitigated by a REMS plan.

I've said it several times. I'm uncomfortable with overly restrictive ETASUs in general because I think access is very important. As Dr. Bell-Perkins said, it's easier to overcome those in urban areas, but there'll definitely be

access issues if we are too strict with ETASU or the REMS.

But I am comfortable with the medication guide, and a communication plan, and with rigorous post-marketing studies, which have been well-outlined by the previous speakers, as well as the limited marketing. At first, I do think that there's going to be a huge buzz around this and that to be able to roll it out slowly and avoid some of the initial commercials, which are going to come down the pike, would probably be a good way to start.

DR. STURMER: I voted B. I was on the fence here, I have to admit. I think this would be a perfect example for something like staggered licensing, but the closest that the FDA has with respect is to vote B but then require a postmarketing study, so that is my suggestion.

The reason to vote B and not C is that there is clearly an unmet need, and there is proven potential benefit. I think we all agree on that. The overall magnitude of the benefit is not

striking, and there is some tendency for the magnitude to be less pronounced in those most severely affected by the condition. And I think that is something that needs to be taken into consideration.

There are serious safety concerns, so my yes is conditional on the requirement for post-approval study with timely assessment of actual risk for some of the most severe adverse outcomes, concussions, accidents, including fatal ones, and pregnancy outcomes in a large proportion of women treated with the drug, for example, using a registry, but there would need to be more discussion about this.

I'm not an expert on REMS, but the REMS with the ETASU, as outlined, using informed consent and provider certification, and if needed, the pharmacy certification, sounds reasonable to me.

DR. LEWIS: Thank you. Everyone else who votes, please remember to say your name before you say what you --

MS. PHILLIPS: Marjorie Shaw Phillips. I

voted B, and I'd like to echo some of Dr. Sturmer's comments about the postmarketing surveillance that's needed. I think it's really important to set realistic expectations for those small subset of patients that are premenopausal who have HSDD. Some of them will get some meaningful benefit for themselves, but it's not a magical little pink pill. And there's going to be a whole lot of women with sexual dysfunction for whom there's no evidence that it's going to benefit them. And there are some potential safety concerns that everyone needs to be aware of.

I also echo the need for a prescriber registry, is something that I don't think is overly restrictive. And as a pharmacist, I don't think there's a benefit to registering the pharmacist or pharmacy, but I do think there's a role for the pharmacist to confirm that it's a registered provider that's had that discussion -- an educated provider that's had the discussion with the patient, and the patient is knowledgeable before the drug is dispensed, and that is an important

safety consideration.

I think this is a case where a patient registry would be very valuable to make sure you captured postmarketing information. One of the things that I think would be very interesting to learn from a postmarketing basis is what the actual success rate and benefit is in both less controlled use as well as the safety in that less controlled use, and what the discontinuation rate might be.

Some of the information that the FDA shared with testosterone that the large majority of individuals that took it discontinued in less than six months and it wasn't a lifetime therapy, really provided a lot of evidence that it had marginal benefit.

We could very well find that this holds a lot of promise but not as much benefit from any of the people that might want to try it. I think that's important information for the public to have along with the long term safety information to make informed decisions going forward.

DR. PERRONE: Jeanmarie Perrone. I voted B,

but I applaud the people who voted C. I think we've moved the needle at this committee towards marginal drug acceptance using REMS as a tool that shifts the risk/benefit towards accepting these and then modifying afterwards. And I hope we're not in a position in a couple of years of more drug withdrawals on that premise and using a postmarketing surveillance specifically to identify the patients who are being identified already in these studies as having adverse outcomes and getting a better profile of who's at risk.

I also favor prescriber education and perhaps a patient and prescriber registry as Dr. Phillips suggested.

DR. GERHARD: Tobias Gerhard. I agree. I also voted B, very difficult B, definitely between B and C. I agree with a lot of the comments that were made before, particularly with Dr. Sturmer's suggestions.

I think quantifying the risk in real-world settings, including in realistic situations with real-world use of alcohol and so on, is absolutely

critical to enable women and their caregivers to make informed decisions because, currently, the risk side isn't quantified sufficiently to really allow informed benefit/risk decisions, but the unmet need seems to be so strong that even for a drug with rather modest benefit, improving the product with strong limitations seems to be the right step at this point.

I think it's very important that these postmarketing requirements can't just be looking at a database four years after the drug has been on the market. This has to be an active registration of patients that will be burdensome and won't be cheap, won't be easy to do. And if that turns out to be infeasible and can't be set up, then I'd rather lean toward C than to see this product kind of unregulated on the market without any assurance that we'll, while it is on the market, really learn what the true risks are and what that means for the benefit/risk balance.

DR. BESCO: My name is Kelly Besco. I also voted for B. Like other members of the panel, I do

have remaining concerns about this medication.

I do believe that a black box warning about the interaction with alcohol should be added to the labeling until we have further studies to better understand the interaction and the effect on the target population.

I believe that a REMS program needs to be a robust and that a patient prescriber agreement form should be added to the REMS program so that there is documentation that the patient has been adequately informed of the potential side effects, interactions, and what I don't think has been previously discussed, what course of action to take should they suffer a fall or injury after a syncopal episode.

I agree with establishing a prescriber certification program to ensure this medication is being used appropriately. As far as the pharmacy burden, being a pharmacist myself in practice and having to respond to these REMS programs, the act of verifying the prescriber certification is quite minimal, and I do not perceive it to be a burden.

I would also be in favor of instituting some sort of 3-month and 6-month post-initiation audit process that would be conducted through assessment of the patient and perhaps that would be done through the creation of a patient registry program so that we could collect additional information on side effects that could be aggregated for further analysis.

DR. LINCOFF: Michael Lincoff. I voted B for the reasons that have all been described, but my main focus is that the REMS approach should focus on making sure marketing correctly describes a proportion of patients that would expect results and correctly highlights that those patients who are not having a results should come off therapy, and focus on a strong contraindication against alcohol, as well as provider certification that emphasizes the correct patient selection.

There certainly seem to be a lot of patients outside of this narrow diagnostic criteria who would benefit as well, but I think that should be the topic of a future trial that would also be able

to characterize the risk and benefit ratio in those patients. I think it may well help but that should be studied and not extrapolated.

DR. LEWIS: Does anyone else have more comments or questions? FDA? Anyone else?

(No response.)

DR. LEWIS: Okay. So thank you all, a remarkable agreement between the B's and C's actually at this point -- I don't think I've ever seen that before -- in terms of the rationale for the vote.

Again, thank you all for your attention. I'm going to ask Dr. Beitz to close us out here.

DR. BEITZ: Thank you. FDA would like to thank Dr. Lewis and the members of the joint committees for their deliberations today on the benefits and risks of flibanserin. FDA would also like to thank the public for taking the time to provide their perspectives regarding their symptoms and the types of treatment benefits that matter most to them.

We recognize that female sexual dysfunction

is a condition with limited treatment options, and we support the development of safe and effective treatments for this condition. We will carefully consider the input we received today as we continue to review this application. Thank you.

Adjournment

DR. LEWIS: We will now adjourn the meeting. Panel members, please remember to drop your name badge off at the registration table on your way out so that it can be recycled. Thank you again.

(Whereupon, at 4:52 p.m., the meeting was adjourned.)